CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CISPLATIN AND GEFITINIB

Dissertation submitted in partial fulfillment of

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APRIL 2016

CERTIFICATE

This is to certify that **Dr. AOAKHUM KICHU** has been a Post Graduate MD Student during the period from June 2013 to April 2016 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled "CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCEDSQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH CISPLATIN AND CISPLATIN" is a bona fide work done by him during the study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

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DECLARATION

I solemnly declare that the dissertation titled "CONCURRENT CHEMO RADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH GEFITINIB AND CISPLATIN", a SINGLE ARM PROSPECTIVE STUDY was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during **March 2014 to August2014** under the guidance and supervision of Prof. Dr N. V. KALAIYARASI.

The Dissertation is submitted to The Tamil Nadu Dr. M. G. R. Medical University towards the partial fulfilment for the award of M.D. Degree (Branch IX) in Radiotherapy.

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Place: Chennai.

Date:

CONTENTS

CONCURRENT CHEMORADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Dr Aoakhum Kichu*, Prof Dr S. Shanmugakumar, Prof Dr N. V. Kalaiyarasi, Dr Baskar, Dr Madhumati, Dr Sundaraesan, Dr Prabagaran, Dr Sanjal, Dr Vijay Karthick

AIMS AND OBJECTIVES:

To assess the immediate Loco regional response rates and to assess the toxicity profile of locally advanced squamous cell carcinoma of the head and neck treated with weekly Cisplatin and Daily Gefitinib

MATERIALS AND METHODOLOGY:

This was a Phase II single arm study where 30 consecutive eligible patients were included in the study. All patients received a total of 66 Gy of Radiation in 2 Gy per fraction along with weekly Cisplatin 30mg/m^2 and daily tablet Gefitinib 250mg throughout the course of radiation. The immediate locoregional response was assessed after 6 weeks by clinical examination and radiological imaging. The toxicity profile of the treatment was assessed with RTOG acute morbidity scoring criteria.

RESULTS

Out of the 30 patients recruited for the study 25 were males and oropharynx and hypopaharynx were the most common subsites. All patients were able to complete the full course of RT and chemotherapy. Overall 76.6% patients had complete response and 23.3% partial response during assessment after 6 weeks of completion of treatment. Oropharyngeal, hypopharyngeal and laryngeal cancers had good response to the treatment. All patients developed some form of mucositis during the treatment but the rates of grade 3 and 4 mucositis were low. Only 1 patient developed the classical skin toxicity associated with the use of gefitinib.

CONCLUSIONS:

Concurrent chemoradiotherapy with cisplatin and Tablet gefitinib in locally advanced head and neck cancer is a feasible treatment alternative with manageable toxicity, good patient compliance and good response to treatment. Large scale study is needed to show a significant benefit of the addition of gefitinib to the standard treatment protocol.

Keywords: concurrent chemoradiation, cisplatin, Gefitinib, anti-EGFR therapy, single arm

INTRODUCTION

Cancer of any site is a dreaded diagnosis for a patient and it has a profound impact, not only on the patients' own physical, emotional well being, but it also affects the lives of those around them. The burden of head and neck cancer in the world is large and significant, being the 6th most common type of cancer overall. In India the incidence is even higher and is one of the most common type of cancer. The incidence also varies according to the geographic distribution and the local habits. Its incidence highly correlates with the abuse of tobacco in its various forms and the synergistic effect of its combination with its partner in crime, alcohol.

There is a general increasing trend in the incidence of cancer worldwide. Developing countries like ours contribute the major portion of the new cancer cases worldwide. High incidence of oral cavity cancer is reported from Australia, India, South Africa and Western Europe[1]. Cancer incidence is highest in India amongst the SAARC countries[2].

Majority of the patients present in the locally advanced stage where they are treated with a combination of all the three major

modalities of oncology- surgery, chemotherapy and radiotherapy. However even with the best of therapy the overall 5 year survival amongst this group hovers around the 50% mark, and it is even less in a developing country like ours. And even with all the recent advances in therapeutics in all the three fields there has been no significant change in the survival.

In India, cancer of the head and neck ranks amongst the second most common in males and the fourth most common in females. Head and neck cancer is the fourth most common cause of death in the 25-69 years age group following cardiovascular disease, respiratory disease and tuberculosis[2]. Hence it is no coincidence that head and neck cancers create a major burden on the country as it effects a population group which forms the major productive part, whether it be economically or socially.

According to a WHO report, at any point there are 2.5 million cancer patients in India of which a third is formed by the head and neck cancer group. This incidence also varies according to the geographic location and the habits of the local people which expose them to the causative agents of cancer, mainly tobacco which can be in various forms like Paan, Gutkha, smoking, etc.

Along with cancer, other non communicable diseases like cardiovascular disease, diabetes, hypertension have emerged as the main cause of morbidity and mortality as compared to the non infectious diseases. Cancer and these other non communicable diseases have become a big public health problem and concern. Hence we are closely catching up with the western population in terms of pattern of disease prevalence.

But our health care system is still lacking behind with many regions not equipped enough to provide the standard treatment that is being followed in the western countries, especially when it comes to cancer. The government has initiated a number of ways to bring about the causes of cancer and means to take preventive measures, especially against the use of tobacco. Advertisements promoting tobacco and its products have been taken off air and warning labels mentioning that use of tobacco causes cancer is displayed on every product containing tobacco. Also the media is being used to create awareness on how use of tobacco leads to cancer.

Inspite of all the aggressive campaign waged against tobacco, the rates of tobacco addiction, especially amongst the younger generation is increasing and as a result the incidence of tobacco related cancer in general and head and neck cancer in particular

continues to show an increase. There is also an increasing number of cancers in the younger adults reflecting the widespread of tobacco products amongst this group.

AETIOLOGY AND RISK FACTORS:

Man is his own worst enemy and he tries again and again in several ways to bring about destruction upon himself. The most common cause of cancer worldwide is the use of tobacco in its various forms. The risk associated with the use of tobacco and cancer is proven beyond doubt. And it is like common knowledge where even the least educated is aware that it can cause cancer and a number of other debilitating diseases. Inspite of this the use of tobacco is rampant and the cancer continues to increase. Here we talk about the various risk factors for head and neck cancer

TOBACCO

The use of tobacco has been documented as early as 1400-1000BC where native American people smoked the plant during special/sacred occasions or seal bargains. They believed it to be a gift from their creator and the exhaled smoke carried the persons' thoughts or prayers to the creator. The use of tobacco was further popularized with the arrival of the Europeans and it was used as a popular trade item. From there it spread throughout the world

where it was smoked mostly for leisure. Now the tobacco industry has become a multibillion dollar industry worldwide.

It is estimated that 43% of cancer deaths are due to tobacco, inactive lifestyles, unhealthy diets, and alcohol consumption[3].Of these, tobacco use is the world's most avoidable cause of cancer. There are 1.2 billion smokers and hundreds of millions of smokeless tobacco users in the world[4,5]. When it comes specifically to head and neck cancer the national cancer institute reported that 85% of the patients had history of tobacco use. The use of tobacco strongly correlates with the development of head and neck squamous cell carcinoma.

SMOKING

Smoking is the most popular form of using tobacco and is prevalent across cultures. Whatever the form or the nomenclature, it basically involves the inhalation of the smoke cause by burning tobacco. The major carcinogens present in tobacco smoke are PAH (polycyclic aromatic hydrocarbons), NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] andNNN(N1-nitroso nor nicotine). Nicotine, the most commonly known ingredient of tobacco by itself is not carcinogenic but it is a psychostimulant and is responsible to

the addictiveness to tobacco, hence leading to repeated exposures to the carcinogenic substances.

Worldwide filtered cigarettes are most commonly used whereas in India the use of Beedis is very common. As compared with cigarettes the carcinogenic load is higher for Beedis as it has a higher puff rate.

SMOKELESS TOBACCO

The use of smokeless tobacco in the form of gutkha, khaini, paan and their combined use with other irritants like arecanuts, slake lime etc contributes a significant amount to the formation of oral cancers.

ALCOHOL

The partner in crime alcoholism is a habit that goes hand in hand with the use of tobacco. More of a lifestyle choice where a person taking either one is more likely to take the other. Its like the addiction to one leads to the addiction to the other, hence it resembles a synergistic relationship. In this context the use of alcohol has a synergistic effect with tobacco enhancing the cancer causing effect.

A meta-analysis from 26 studies of oral and pharyngeal cancers found that consumption of 25, 50, or 100 g pure alcohol/day1 was associated with a pooled relative risk (RR) of 1.75, 2.85, and 6.01, respectively, of oral and pharyngeal cancer. Also the use of alcohol leads to a variety of other health problems which in turn affects the cancer outcome and survival.

ROLE OF HUMAN PAPILLOMA VIRUS

The role of HPV infection and cancer is well proven in cervical cancer. And now its role is being extensively studied in head and neck cancer also. In several studies the presence of the HPV virus in aquamous cell carcinoma of the head and neck is well documented with a range of around 30-35%. The rate is even higher in oropharyngeal cancers.HPV infection is proved to be one of the causative factor in SCCHN.

As in cervical cancer, the viral genes are incorporated into the host genome leading to the production of the oncoproteins E6 and E7 which inactivates the P53 and initiates carcinogenesis. Overall such patients have a better response to chemotherapy and radiation and has a better prognosis as compared to HPV negative tumours.

OTHER RISK FACTORS

A variety of other risk factors like sharp tooth, iron deficiency anemia (Plummer vinson syndrome), vitamin A deficiency, spicy foods etc are implicated in the development of cancer. Rarely head and neck cancer may develop in the presence of genetic abnormalities like Fanconi Anemia (FA), Ataxia Telangiectasia, Blooms Syndrome, & Li-Fraumeni Syndrome etc.

CLINICAL FEATURES AND PRESENTATION

The symptoms depend on the site of the primary and the nodal involvement. Tumors of the oral cavity usually present as an ulcer or growth. Non healing ulcers are also a common presentation. Tumours in the pharynx can lead to dysphagia or odynophagia. Laryngeal cancers presents with hoarseness or change in voice, difficulty in breathing. Many a times, patient came with a complaint of a swelling in the neck due to metastasis to lymph nodes.

HISTOLOGICAL CLASSIFICATION

By far the most common histology is squamous cell carcinoma and its variants. Squamous cell carcinoma is classically divided into three. Well differentiated, moderately differentiated and poorly differentiated. Tis classification is based on the degree

of keratinisation of the cells. And it is well known that as the tumor becomes less differentiated, the prognosis also worsens. The rest are adenocarcinomas salivary gland tumours, melanomas, lymphomas, sarcomas etc.

SYMPTOMS:

Most common presenting symptom is ulcer(or ulceroprolifertive lesion) followed by pain, difficulty in swallowing (dysphagia), pain during swallowing (odynophagia), difficulty in breathing (dyspnea), change in voice, and neck swelling because of lymph nodal involvement. Other generalized symptoms are cough, weight loss, loss of appetite may cause further detoriation with treatment like concurrent chemoradiation. Nutritional status of the patient plays a major role in treatment outcome.

In advanced stages, patients present with large painful masses and symptoms due to spread to adjacent structures. Many patients also have a poor nutritional status and general at the time of presentation which can have a big part to play in deciding the treatment policy. It is also important to assess the patients mental, social and emotional

WORK UP OF THE PATIENT

The work up of the patient before the deciding the treatment policy is very important. A proper history and clinical examination is a must. Assessment of the general condition of the patient should involve the measurement of the height and weight, the presence of anemia and other comorbities. Frequently, due to the common use of tobacco and alcohol in such patients, many of them have other comorbid conditions.

Routine blood investigations are a must to check for anemia and assess the patients' bone marrow reserve. To assess the liver and the renal functions. It is also important to do the viral markers like HIV, Hepatitis B, C etc. ENT examinations in the form of Indirect and direct laryngoscopy, video laryngoscopy, diagnostic nasal endoscopy etc are all important investigations. This helps in assessing the primary lesion and also helps to look for other malignancies as the entire aerodigestive tract is exposed to the carcinogens, causing field cancerisation. In the same way, a upper GI Endoscopy also will provide additional information.

A CT and/or MRI of the head and neck is a must to see the extent of the primary disease and the nodal burden which is important for staging as well as planning of Radiotherapy as well as planning for the surgery. An imaging of the chest either in the form of a plain X-ray or CT or MRI can be if clinically indicated to rule out metastasis to the lung and also to see for and co-morbid lung condition. A PET scan may be considered for stage III-IV diseases and in those with large nodal disease in the lower neck.

OVERVIEW OF TREATMENT FOR HEAD AND NECK CANCER

The treatment of cancer has evolved and is still evolving. All the three major fields in cancer treatment have undergone major changes throughout the ages. However the management of head and neck cancer is complex. It requires a multi-disciplinary approach where inputs from all the specialities are required to design a optimum treatment for the patient. Also it should be an individualized treatment taking into consideration not only the stage of the disease but also the performance status and co-morbidities. The patient should be looked at as a whole.

While it is important not to compromise on the oncological principles, the cosmetic and functional outcome should also not be

ignored. Specially considering that the face is the representation of a person, even slight alterations can cause a lot of psychological trauma. Also we are dealing with an area which required for a lot of functions like speaking, respiration, eating, emotional expressions, etc are all related with the face. So it is imperative that the treatment should allow the person to live as normal a live as possible without compromising on the disease control and survival.

Hence it is a fine balance that has to be achieved. Even though the management of head and neck cancer has come a long way, the optimum is yet to be achieved. Finally the patients' wishes have to be taken into consideration after proper explanations about the pros and cons of each modality of treatment.

SURGERY

It is the oldest modality in the treatment of cancer. Emerging from the history of cancer treatment surgery plays a major role. For ages, surgery has been the primary and only modality. From cutting out whatever growth is seen to now where a adequate margins are given along with reconstruction wherever possible ensuring the best cosmetic and functional outcome, surgery has come a long way. And with the development of robotic surgery, it will only lead to better outcomes.

It is important that all cases should be evaluated by a surgical oncologist before treatment. And a coordinated effort with the medical and radiation oncologist and other specialist like plastic and ENT surgeons is needed.

Surgery is the modality of choice in early stage cancers especially of the oral cavity. However in sites like the hypopharynx, larynx, where the resection of the tumor is difficult or may result in significant loss of function, other approaches like RT can be considered.

A decision has to be made as to whether the tumor is resectable or not. Resectable basically means to be able to remove the whole tumor along with adequate margins. Adequate margins means a margin of 1.5-2cm. If the margin of is less than 0.5cm it is termed as a close margin. Positive margin means the presence of tumor or carcinoma in situ component at the resected margin.

However the term resectability and unresectability are relative terms, depending on the surgeons capabilities and experience. A tumor that may appear to be unresectable to one may be resecatable to the other.

A patients' cancer may be termed unresectable if a surgeon and/or his team feels the cannot remove all gross tumor on anatomic grounds or if they are certain local control will not be achieved after surgery (even with the addition of RT to the treatment approach). These tumors usually involve the cervical vertebrae, brachial plexus, deep muscles of the neck or the carotid artery. Also tumor involvement of certain sites associated with a poor prognosis like direct extension of disease to involve the external skin, direct extension to the mediastinal structures or prevertebral fascia makes them unresectable.

Finally it is important to distinguish unresectable tumours from inoperable tumors, where even though the primary tumor is resectable the general condition of the patient does not allow for a operative procedure. Additionally a subgroup of patients will refuse surgical intervention, but these should not be termed as unresectable.

In patients with distant metastasis, even though the locoregional disease may be surgically treatable, such patient are usually treated as though the primary tumour is unresectable.

There is also a subgroup of patients who can be adequately treated without surgery. They form an important group. RT alone or in combination with chemotherapy may offer a more attractive approach to these cancers without the morbidities of surgery.

Addressing the nodal disease is also very important as they are frequent sites for disease failure. Historically neck dissection have been classified as radical or modified.

Radical neck dissection involves removal of the superficial and deep cervical fascia with its enclosed lymph nodes (levels I to V). Along with that the sternocleidomastoid muscle, the omohyoid muscle, the internal and external jugular veins, cranial nerve XI, and the submandibular gland are also removed.

Modified procedures involved the preservation of structures like the sternocleidomastoid muscle, Jugular vein and spinal accessory nerve.

Type I—cranial nerve XI is spared;

Type II—cranial nerve XI and the internal jugular vein are spared;

Type III (functional)—cranial nerve XI, the internal jugular vein, and the sternocleidomastoid muscle are spared.

Another term is selective neck dissection where the lymph node levels at greatest risk are removed selectively.

A new nomenclature has been defined where neck dissections are classified into either comprehensive or selective. In comprehensive neck dissection, all lymph node levels that would be removed in a classical radical neck dissection are removed i.e. level I-V. And it doesn't matter whether the other three structures, the sternocleidomastoid, the jugular vein or the cranial nerve XI are removed or not.

In selective neck dissection, only those with a high risk for involvement from that particular primary are dissected. It is mostly recommended for N0 disease. For example, for a oral cavity lesion with a N0 disease, a selective neck dissection would include removal of nodes found above the omohyoid, commonly level I-III and sometimes the superior part of level V. For a laryngeal or pharyngeal primary, the recommendation is removal of level II-IV and and level VI when appropriate. For infraglottic cancers an elective dissection of the level VI nodes is considered.

In general <10% of head and neck cancer patients who do not have any clinically positive nodes will have nodal metastasis beyond the confines of a appropriate selective neck dissection. Hence in most patients a selective neck dissection is more than appropriate to achieve a good disease control.

In general a comprehensive nodal dissection is recommended for those with large nodal burden, like N3 disease. Selective neck dissection is recommended for clinically N0 disease. In certain patients with N1 or N2 disease selective neck dissection may be appropriate and can reduce the morbidity in these patients.

Another important aspect is to whether to proceed with a ipsilateral neck dissection or a bilateral one. Bilateral dissection is recommended for tumors at or near the midline and for those with bilateral drainage.

Another important role of surgery is in the form of a salvage treatment. In patients who have been treated with non surgical methods like chemo radiation, if there is a failure to control the disease, then surgical excision of the residual or recurrent lesion can be done. Such patients have to be kept under careful follow-up so that the disease can be caught early and managed appropriately.

RADIOTHERAPY

The field of radiation oncology has come a long way since the discovery of X-rays by William Roentgen in 1895. Then the realization that these X-rays can be used for killing tumor cells and also the discovery of radium by Marie Curie were the initial stages from where Radiotherapy has grown into one of the major arms for the treatment of cancer.

Radiation can be used as the primary modality or as an adjunct to surgery. The main advantage of radiation is that it allows for the organ to be preserved resulting in less morbidity as compared to surgery. Radiation can be administered alone or in combination with chemotherapy and both have a synergistic effect. It can be given as a pre-operative treatment to allow for downsizing of the tumor resulting in better resectability and decreasing volume of tissue that needs to be resected.

It can be administered after surgery to produce a better locoregional control especially in those with locally advanced disease, with positive margins or extra-capsular extension, in those with lymphovascular invasion, deep infiltration of tumor all of which have a higher chance of recurrence.

Radiation can be the only form of treatment in early stage small volume lesions where it achieves local control comparable with that of surgery. And in those with locally advanced cancers where surgery is not possible or where a organ and functional preservation is desired, radiation along with the combination of chemotherapy can be used.

Radiation can be delivered in the form of external beam radiation (EBRT) or brachytherapy. The aim of radiation therapy has been to deliver the maximum possible dose to the tumor and the minimum to the normal tissues. With the developments in the radiation delivery systems we are now able to more closely adhere to this philosophy. From 2D RT to 3D conformal RT to Intensity modulated RT, we are able to better spare the normal tissues from the deleterious effects of RT while at the same time delivering a substantial dose to the tumor.

There are now different methods of delivering RT which has been modified from the conventional fractionation. Conventional fractionation is 2 Gy per day for 5 days a week. The available data suggests that at least 1000cGy has to be delivered in fractionated schedules per week tom achieve a good tumor control. The altered fractionations are hyperfractionation and accelerated fraction.

In Hyperfractionated RT there is an increase in the number of fractionations, a significant increase in the dose, a significant reduction in the dose per fraction and no significant change in the overall treatment time. It exploits the different sensitivities of the tumor cells and normal cells to RT and the ability of the two cell types to repair the damage caused by radiation.

In accelerated Fractionation the overall treatment time is decreased so as to negate the accelerated repopulation that takes place in tumour cells aftyer the initial exposure to RT. It can be pure, where conventional dose fractionation is used. It can be hybrid, where the dose fractionation is altered.

In a major study conducted by the RTOG conventional fracxtionation was compared with hyperfractionated RT, split course accelerated RT and concomitant boost regimen. In this study the found that Concomitant boost and hyperfractionation group yielded a significantly better control as compared to the standard conventional fractionation. Split course RT did not provide any significant advantage. A important point to be noted was that the altered regimens had significantly higher acute toxicity rates. However the late complication rates were similar in all the groups.

Brachytherapy is another way of therapy where the radiation source is kept in close proximity to the tumour. It canbe used as a form of boost to the tumour after initial EBRT or it can be used alone in small early stage disease. Its advantage is that the dose delivered is highly conformal and there is minimal damage to the adjacent normal tissue.

Another area where radiation plays a major role is in the palliative setting. A significant proportion of patients, especially in our country where many patients present in the very advanced stage where surgical resection is not possible and we cant expect to achieve a cure with our chemoradiation. Also many of these patients present with a poor general condition where the patient will not be able to tolerate all the radical procedures. In such patients palliative radiation can be given to relieve symptoms like pain, bleeding, etc.

CHEMOTHERAPY

Chemotherapy too plays a very important role in the management of head and neck cancer. In the curative setting it acts as a radiosensitiser, enhancing the effects of radiation leading to more cell kill. Also it too has its own cytotoxic effect leading to an increased response when given together with radiation. It also takes

care of any microscopic, undetected metastasis at a distant site which might not be detected at the initial presentation.

There is a recent increasing trend in the use of neo-adjuvant chemotherapy before starting the primary treatment. This helps to decrease the burden of the disease leading to better resectability or better response to radiation. However multiple large scale trials have not shown any consistent benefit with the use of induction chemotherapy on the overall outcome. However with the development o newer drugs and newer combination of chemotherapy, induction chemotherapy remains an attractive option.

Chemotherapy is also indicated in combination with radiotherapy in those with a positive margins or extracapsular extension in the post operative histopatholgy. In patients with recurrent or metastatic disease not amenable for a curative attempt by surgery or radiation, chemotherapy plays a major role. Numerous trials have shown survival benefit with the use of chemotherapy in such patients. But it is important to balance between the expected benefit and the associated toxicity of chemotherapy.

EFGR AND TARGETED THERAPY

The Epidermal Growth factor receptor (EGFR) is a cell membrane receptor that belongs to the ErbB family of receptors. The ErbB family consist of four closely related receptor tyrosine kinases

- EGFR (ErbB-1)
- HER2 (ErbB-2)
- Her3 (ErbB-3)
- Her4 (ErbB4)

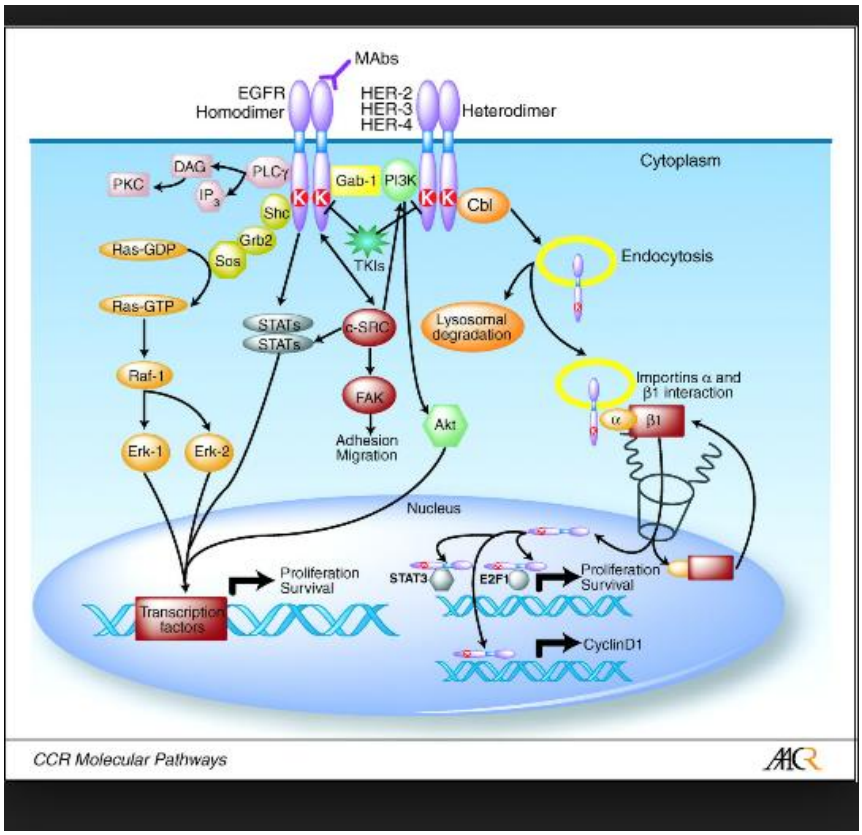

Figure 1. The EFGR pathway

EGFR is normally present in cells and helps to perform a number of functions. It was first discovered by Stanley Cohen of Vanderbilt University. It is activated by a number of ligands including the epidermal growth factor and transforming growth factor – alpha. After the binding of the ligand it forms a homodimer which leads to activation and autophosphorylation of the tyrosine kinase residues in the intracellular domain of the receptor. It can also form heterodimers with other members of the ErbB family leading to activation of the tyrosine kinases. EGFR are can also be activated in the absence of ligands like in the setting of mutations or stressful conditions like under radiation.

Once the tyrosine kinases are activated it initiates a number of downstream pathways like the MAPK, Akt and JNK pathways which eventually lead to DNA synthesis and cell proliferation. In tumor cells it can lead to cell proliferation, tumor invasion, metastases, increased cell survival and anti apoptotic signals.

It is well known that EGFR over expression is seen in over 90% of head and neck cancers. And high levels of EGFR are associated with decreased survival, resistance to radiotherapy, locoregional failure and increased rate of distant metastases.

EGFR was proposed as a pathway for targeted therapy based on intial researches that EGFR was frequently over expressed in epithelial tumors. With improved understanding of the oncogenic role of EGFR,its mechanism of action, the discovery of somatic mutations and other mutations in the components of the singling pathway, the prospect of targeting this receptor has become even more attractive.

Basically there are two groups of drugs against EGFR, they are the monoclonal antibodies MABs and the Tyrosine Kinase Inhibitors TKIs. The first of the monoclonal antibodies was cetuximab and other subsequent drugs include panitumumab, nimotuzomab. They target the extracellular receptor ligand binding site preventing the activation of thee receptor and its activation. The TKIs are smaller molecules that target the intracellular tyrosine kinases that are activated through the extracellular binding of the ligand to the receptor. The activation of the tyrosine kinases initiates a series of pathways that eventually lead to the action of EGFR.

These targeted therapies have proven its role in lung cancer where the TKIs like Gefitinib and Erlotinib and more recently Afatinib has shown to improve the progression free survival and

also the overall survival in patients having mutations in the EGFR gene. Several trials have proven effect of anti-EGFR therapy.

The anti EGFR drugs have also been tried in a number of other sites showing a varied results. It has been use in cancers of the colorectum, pancreas, CNS, etc. In head and cancer cetuximab was the first drug that was shown to have improved benefit in the setting of locally advanced head and neck cancer when it was added to Radiation. It has also improved the overall survival in the recurrent and metastatic head and neck cancer when used in combination of chemotherapy. Other anti EGFR drugs are being investigated in various trials across the world.

DESCRIPTION OF THE DRUGS

The drugs that are used in this trial are Cisplatin and Gefitinib.

CISPLATIN

Cis-diaaminedichloroplatinum is a platinum analogue that covalently binds to DNA analogue with preferential binding to the N-7 position of guanine and adenosine and causus the production of crosslinks that eventually lead to inhibition in DNA synthesis. It can also bind to nuclear cytoplasmic proteins resulting in cytotoxic

effects. Apart from its cytotoxic effect it also acts as a radiosensitizer for radiation.

It is given parenterally and is widely distributed in plasma with less than 10% remaining in the plasma after I hour of infusion. Inside the cells it undergoes a aquation reaction where a chlrode molecule is replaced by a water molecule leading to the production of a highly reactive species which causes the cell damage. It is excreted mainly through the kidney.

The main toxicities of cisplatin include

- **Nephrotoxicity**: due to its activity on the renal microtubules, it cacuses renal damage. Dose limiting in upto 35-40% of patients. It is generally reversible however the effect is dose related and can lead to acute as well as chronic renal failure.

- **Myelosuppresion**: it is seen in 25-30% of patients with all the three cel lineages equally effected. As the dose is increased, leucopenia and thrombocytopenia are more pronounced.

- **Ototoxicity:** is also dose related resulting in high frequency hearing loss and tinnitus

- **Neurotoxicity:** this is dose related most commonly resulting in in peripheral sensory neuropathy. Stocking and glove pattern of paresthesias and numbness are classically seen. Motor function defect, enceplhalopathy and seizures can also occur

- **Nausea and vomiting:** it is also a common problem with the use of cisplatin. It can occur immediately- acute form ot after 24 hours of infusion- delayed form.

- **Other toxicities** like alopecia, ocular toxicity hypersensitivity, azoospermia, sterility etc can also be seen

Cisplatin forms the first line of chemotherapy in a number of cancers including head and neck cancer, lung cancer, blader cancer, ovarian and testicular cancer, esophageal cancers, etc. the dose usually ranges from 75-100 mg/m^2 in a three weekly regimen to 30-40mg/m^2 with a weekly regimen.

GEFITINIB

Gefitinib is a small molecule tyrosine kinase inhibitor that has specific activity against the EGFR Tyrosine kinase. It causes inhibition of EGFR autophosphorylation and inhibition of the

EGFR tyrosine kinase that leads to inhibition of critical mitogenic and anti-apoptotic signals involve in cell proliferation, metastasis, angiogenesis and response to chemoradiation.

The oral absorption of gefitinib is slow and reaches a peak plasma concentration by 3-7 hours of intake. The oral bioavailability is approximately 60%. It is extensively bound to plasma proteins an extenxively distributed throughout the tissue. A steady state drug concentration is reached in 7-10 days.

It is metabolized in the liver largely by the CYP3A4 microsomal enzyme. The main metabolite is O-desmethyl piperazine derivative which is significantly less potent than the parent drug. Most of the drug I excreted in the faeces. Only about 4% are excrete through renal secretion. The terminal half life of the parent drug is 48 hours.

Gefitinib is mostly used in lung cancers having the EGFR mutation. Its role in other epithelial malignancies are still under trial. The commonly used dose of gefitinib is 250 mg per oral daily.

Gefitinib is a relatively safe drug having ,minimal see effects. It mostly results in pruritus, dry skin, with a mainly pustular acneiform skin rash. The rash is most commonly seen in the face,

neck and other sun expose areas of the skin. The skin rash is usually less as compared with that seen with the monoclonal antibodies. The skin rash is mostly self-limiting and usually resolves without without scarring, it can negatively impact the treatment compliance and the quality of life. It exposes the skin to infections and can also cause treatment discontinuation or dos modification, hence it can affect the outcome.

The EGF Receptor is normally expressed in the epidermis, sebaceous glands and hair follicular epithelium where it plays a number of important roles for maintaining the health of the skin. The exact mechanism of how skin rash is produce is not fully known but a possible mechanism is described. With the inhibition of the EGFR it causes follicular occlusion and rupture because of premature epithelial differentiation an it also causes an increase in the genes that initiate inflammation, apoptosis and cell attachment. With this defect it also allows for bacterial infection and growth to occur which worsens the situation.

The development of the rash usually follows a well regularized timeline

1) First week- sensory disturbance with erythema and edema

2) Weeks 1-3: papulopustular eroptions manifest

3) Week 4- crusting of the lesions

4) Week4-6: even with successful treatment, the erythema and dry skin may continue to persist General measures for the prevention and management of rash include:

- To take appropriate sun protection. Exposure to sun increases the severity of the rash
- avoid activities and skin care products that causes of skin like taking long hot showers, alcohol based or perfumed products, and other acne medications. Greasy ointments are to be avoided. Moisturizers and alcohol free emollient creams can be used
- topical clindamycin 2% is recommended for mild to moderate grade skin rash.
- Medium potency steroids like 1% hydrocortisone can be used for mild to severe skin rash as it inhibits the inflammation
- In moderate to severe skin rash, oral antibiotics like minocycline or doxycycline are recommended in addition to the topical antibiotics

- Deferring of the anti-EGFR if the symptoms do not improve within 1-2 weeks

- If the rash is severely symptomatic with necrosis, blistering petechial and purpuric lesions, a expert opinion from the dermatologist should be obtained.

Other toxicities of gefitinib include elevations in blood pressure, especially in those with hypertension, increase in the liver enzymes, anorexia, mild nausea or vomiting, and rarely hemoptysis and GI hemorrhage.

REVIEW OF LITERATURE

In patients with locally advanced head and neck cancer not amenalble ti surgery radiation along with chemotherapy has emerged as the treatment modality of choice. The most commonly used method of delivering radiation is the conventional fractionation\ method where 200cGY is delivered 5 times per week. This method was first widely used by **Fletcher et al**. This method was thought to provide the best compromise between the tumour cell kill and normal tissue sparing allowing sufficient time for the recovery of the normal cells from the effects of radiation. But now with better understanding of the radiobiology of the tumor as well the normal cells new forms of treatment have been devised that allows for better therapeutic ratio to be attained i.e. increased tumour control probability and decreased normal tissue toxicity. These are the modified fractionation schedules.

The **EORTC in their landmark trial 2279** compared conventional fractionation with hyperfractionated RT. Here patients were divided into two groups with one arm receiving the conventional fractionation of **70 Gy in 2Gy** per fraction five fractions per week while the other arm received hyperfractionated

RT of **80.5 Gy** delivered in 70 fractions, **1.15 Gy** per fraction delivered as twice daily schedules with a interval of 4-6 hours between the fractions. At the end of the trial there was a 219% significant increase in the locoregional control and a non statistically significant improvement in the overall survival. The acute toxicity was enhanced in the hyperfractionated arm but the late toxicity between the two arms was similar .[6]

In another trial **(Danish DAHANCA 8 trial)** accelerated radiotherapy was compared with conventional RT. In this trial there was a **15%** improvement in the locoregional control and as with the hyperfractionated RT trial, there was an increase in the acute toxicities but the late toxicities were similar.[7]

Till now the combination of chemotherapy with radiation has provided the best results in terms of tumour control and overall survival. There are several trials that have investigated the use of chemotherapy along with radiation using a variety of different chemo drugs and RT schedules and altering the timing of when the patient is exposed to the chemotherapy. An important meta-analysis of these trials is the **MACH-NC Trial** which proved that the concurrent use of chemotherapy along with radiation has the best results.

MACH- NC

The initial publication of the **MACH – NC (meta- analysis of chemotherapy in headand neck**) study analysed data from RCTs from 1965 to 1993 and published the findings. Since then an update including 24 new trials have been published. Data of abuout 10,000 patients from 63 trials were analysed. In the control arm the overall survival was 32 % at 5 years. It was found that the use of chemotherapy at any time of treatment resulted in an absolute benefit of 4% which meant that it increased the 5 year survival from 32% to 36%[8].

The analysis also found that the timing of chemotherapy had a significant impact on the overall outcome. The greatest benefit was seen with the use of chemotherapy concurrently with an absolute benefit of 8% improvement in the overall survival at the end of 5 years. The use of adjuvant chemotherapy resulted in a absolute benefit of 1% while the use of induction chemotherapy resulted in a benefit of 2%.

In the updated MACH-NC which included trials performed from 1993-2000 and included 24 new trials the absolute benefit that was seen with the use of chemotherapy did not change i.e. 4%. And as in the previous publication the benefit od neoadjuvant and

adjuvant chemotherapy is not clear. And irrespective of the type of fractionation use the benefit seen with the use of concurrent chemoradiation is seen. Another important finding is that cisplatin based chemotherapy had the most benefit and there was no significant difference in those receiving single agent cisplatin or combined chemotherapy. Also the effect of chemotherapy is less pronounced in older individuals, specially in those older than 70 years.

Although three weekly cisplatin is the standard form of delivering cisplatin, several trials have emerged that has compared three weekly cisplatin with weekly cisplatin and found that there was no significant difference between the two in terms of treatment outcome. Also high dose cisplatin is associated with a significantly higher toxicity and patients compliance is low, hence weekly cisplatin which is more better tolerated may become the treatment of choice.

WEEKLY CISPLATIN TRIALS

In a study by **Akihiro Homo et al**, where patients with locally advanced head and neck cancer were treated with conventional RT and weekly cisplatin of 40mg/m2 the overall

survival rate and disease free survival were 93.7% and 88% respectively. The toxicities were well manageable.[9]

In a single institution experience presented by the **Basket University in ASCO 2011,** they found that there was no significant difference in the median overall survival, the locoregional failure rate and the distant relapse rates in patients treanted with weekly cisplatin as compared with those treated with the three weekly regimen. They conclude that theweekly regimen of cisplatin is as effective as the three weekly regimen.[10]

In an Indian study conducted at the **Tata Memorial Hospital** where 264 patients of locally advanced headn and neck squamous cell carcinoma were treated with conventional RT and weekly cisplatin dose of 30mg/m^2. They conclude that weekly cisplatin has moderate efficacy with acceptable toxicity and has the potential to become an optimal therapeutic regimen.[11]

A study conducted by Ho and his colleagues in 2008 compare three weekly cisplatin vs weekly regimen in locally advanced head and neck cancer. They found that the three weekly regimen was associated with more treatment delays and the patients received a lesser cumulative dose as compared with those getting the weekly

regimen. Majority of the patients getting the weekly regimen were able to achieve a high cumulative dose of 240mg/m^2 or more as compared with those in the three weekly regimen.

In a study conducted at the **University of Wisconsin Tray Nor et al** patients with locally advanced head and neck cancer were treated with a weekly cisplatin dose of 30mg/m^2 along with conventionally fractionated radiation of 70 Gy delivered by IMRT. The locoregional control and the median overall survival was 85.5% and 86.9% respectively. The conclusion was that weely cisplatin is well tolerated and is efficacious.[12]

Finally it can be said that the compliance is a significant problem with the standard three weekly cisplatin. Almost a third of the patients do not receive all the scheduled cycles and subset analyses shows that two doses is as efficacious as three doses of three weekly cisplatin. Some trials conducted like the **RTOG 0129** suggest that there may be a minimal threshold in the cumulative dose of approximately **200mg/m^2** that is required to obtain a maximal benefit when used concurrently with radiation. Schedules that administer chemotherapy more frequently throughout the course of RT deliver approximately the same cumulative dose as would be achieved through two bolus doses of cisplatin without the

excessive toxicity seen with the administration of such a high dose of cisplatin as a bolus.

TRIALS USING GEFITINIB

In a phase I trial conducted by **Changhu Chen et al**, where Gefitinib with two doses of 250mg and 500mg was combined weekly cispatin of 30mg/m^2 and RT with concomitant boost they concluded that the use of daily gefitinib with concomitant boost RT or concurrent chemoradiotherapy was well tolerated. Also the protracted administration of gefitinib upto 2 years at 250mg daily was well tolerated. [13]

Cohen et al performed a study two cycles of carboplatin with paclitaxel induction chemotherapy followed by a split course CCRT with %Fu, hydroxyurea and twice daily hyperfractionated RT along with daily gefitinib after which Gefitinib was continued for two years. CR rate after CCRT was 90%. After median follow-up of 3.5years, 4-year overall, progression-free, and disease-specific survival rates were 74%, 72%, and89%, respectively. High gene copy of EGFR was associated with worse overall survival. The authors conclude that Gefitinib can be administered with hyperfractionated RT followed by maintenance therapy for at least

2 years, with outcomes that compare favourably with prior experience.[14]

Hainsworth et al evaluate the feasibility, toxicity and the efficacy of the drug Gefitinib added to first line combined modality therapy of locally advanced hea and neck squamus cell carcinoma. Only patients whose expecte cure rates were low were included in the study. Patients received a six week induction course of Docetaxel, 5 FU and Gefitinib 250mg. After that patients received concurrent chemoradiotherapy with weekly docetaxel and daily gefitinib. After the completion of RT Gefitinib was continued till disease progression or till a maximum of two years was achieved. The estimated 3-year progression-free was 41% and overall survival rate was 54%. The authors concluded that the addition of gefitinib had a moderate increase in the toxicity especially in the induction phase and although the regimen was efficacious the survival rates were similar. The role of EGFR inhibitors in first line combined modality therapy in patients with advanced head and neck cancer remains undefined. [15]

Bella Pajares et al performed a study where they compared conventional chemoradiation with cisplatin vs RT with Gefitinib in patients who were positive for HPV viral infection. They found

after a median follow up of 35 months those who were p16 positive showed an improved outcome with RT and Gefitinib compared with those treated with RT and cisplatin.(2-year OS 88% vs. 60%, HR 0.18; 95% CI 0.04 to 0.88; p = 0.01; and 2-year DFS 75% vs. 47%, HR 0.17; 95% CI 0.03 to 0.8; p = 0.01). There were no significant differences observed in those who were p16 negative (2-year OS 56% vs. 53%, HR 0.97; 95%CI 0.55 to 1.7; p = 0.9; and 2- year DFS 43% vs. 45%, HR 0.99; 95% CI 0.57 to 1.7; p = 0.9). they conclude that p16 positive tumors may benefit more from RT plus EGFR inhibitor than conventional chemoRT.[16]

Bhattacharya et al performed a prospective randomised control study in Indian patients where they compared chemoradiation using weekly cisplatin 30mg/m^2 and conventional fractionated RT to a dose of 66 Gy with or without the addition Gefitinib. They concluded that addition of Gefitinib to standard concurrent cisplatin based chemoradiation was well−tolerated, and had better overall response and DFS (at 1 year) with addition of Gefitinib as compared to standard concurrent chemoradiation.[17]

Choudhury et al also performed another study where the standard concurrent chemoradiation with 60-66GY RT and three weekly cisplatin was compared with the regimen along with Daily

Gefitinib. At a median follow up of 26 months the response rates was statistically more in the Gefitinib arm (91.6% vs 69.5%) and had the patients had a longer Disease free survival. The authors concluded that the addition of gefitinib to the conventional chemoradiation improved the overall response rates and the DFS, with an increase in toxicity which was manageable.[18]

In another trial by **Charu Singh**, patients of locally advanced head and neck cancer were divided into two groups, one group received concurrent chemoradiation with 70 Gy RT and weekly cisplatin 30mg/m^2 and the other group received additional Gefitinib 250mg daily. The overall response rates were 88% Vs 79% in favour of the Gefiutinib arm. 79% of the patients achieved a complete response in the Gefitinib arm as compared to 62 % in the other arm. Except for dermatitis there was no significant difference in the toxicity profile of the two arms. The author concluded that targeted therapy with Gefitinib and chemoradiation is well tolerated with some enhanced but manageable toxicity and has shown to improve the local control.[19]

AIMS & OBJECTIVES

The aim of this study was to evaluate the use of Gefitinib and weekly Cisplatin concurrently with conventional radiation in locally advanced squamous cell carcinoma of head and neck.

PRIMARY OBJECTIVE:

To assess the immediate locoregional response in patients with locally advanced head and neck cancer treated with concurrent chemoradiation using weekly cisplatin and Tablet Gefitinib.

SECONDARY OBJECTIVE:

To assess the acute toxicity of the treatment regimen.

MATERIALS AND METHODS

STUDY DESIGN

Single arm prospective study with a Phase II design.

STUDY DURATION

March, 2015– August, 2015

STUDY CENTRE

Department of Radiotherapy,Barnard Institute of Radiology & Oncology, Madras Medical college, Chennai.

SAMPLE SIZE:

30 patients presenting to the department of Radiotherapy with locally advanced head and neck squamous cell carcinoma fulfilling the inclusion criteria were recruited for the study.

ETHICAL COMMITTEE APPROVAL

Approval from the institute ethical committee was obtained on 11.03.2014.

INFORMED PATIENT CONSENT:

All the patients recruited for the study were explained in detail about the study, the type of treatment and the advantages and disadvantages of the treatment. Once the patient had understood

and their queries answered informed consent was obtained from the patient, agreeing for their participation in the study. For better understanding the informed consent was in the regional language- Tamil.

INCLUSION CRITERIA

- Biopsy proven newly diagnosed squamous cell carcinoma of the head and neck
- Primary tumor sites: oral cavity, oropharynx, hypopharynx, larynx
- Stage III or IVA disease without any evidence of distant metastases
- Age < 70 years
- ECOG performance Status ≤2
- No previous surgery or radiotherapy or chemotherapy
- Adequate bone marrow reserve and normal hepatic and renal functions
- No associated comorbidities

- Signed informed consent prior to initiation of protocol specific procedures

EXCLUSION CRITERIA

- Non squamous histology
- Tumours of the nasal cavity, paranasal sinuses, nasopharynx, salivary glands
- Previously received treatment for any other malignancy
- Inadequate hepatic and renal functions and bone marrow reserve
- Patients not consenting for chemotherapy at any point in the treatment

PRE TREATMENT WORK UP

- Thorough history and clinical examination
- Upper aerodigestive tract evaluation by direct and indirect laryngoscopy, anterior and posterior rhinoscopy and endoscopy if indicated to know the extent of disease and rule out a second primary.
- Biopsy from the primary tumor or fine needle aspiration cytology from the metastatic lymph node.

- Blood grouping and typing.
- Complete blood count, Renal function test, Liver function test.
- CT scan of the head and neck, plain and contrast, before initiating treatment and also after treatment for response assessment.
- Chest X ray
- Cardiac evaluation and fitness.
- Naso-gastric tube insertion if indicated
- Dental prophylaxis including scaling, dental filling and extraction if required.
- Tumour stage, performance status and weight were recorded, and body surface area were recorded
- Staging was done based on American Joint Committee staging manual 7^{th} edition
- Weekly CBC, RFT, LFT before each cycle of chemotherapy.

GENERAL PREPARATION OF THE PATIENT

Once the patients were enrolled in the study they were explained about the procedures involved. For the patients that had history of smoking or use of other forms of tobacco, and history of alcoholism, they were expressly counseled about the need for quitting such habits if they had not already done so. They were explained that the use of tobacco and alcohol could hamper the treatment outcome. They were also counseled that the continued use of these things put them at a higher risk for recurrence of the tumor and also the risk of having a new cancer at other parts of the body.

Most of the patients had poor oral hygiene and they were advised dental evaluation. As per the requirements dental scaling, filling and extraction of teeth were done. A minimum gap of 14 days was kept between the last dental extraction and the start of radiation and chemotherapy to allow sufficient time for healing to take place.

Patients were also explained about the side effects of chemoradiation in the head and neck specially mucositis. The importance of keeping a good oral hygiene was stressed upon. Patients were advised to gargle their mouth atleast 5-6 times per day. If commercially available mouth wash were affordable, the

patients used them. Otherwise they were taught on how to make their mouth wash by dissolving soda bicarbonate and some salt in water and use it regularly. Patients were advised to avoid toothbrushes having hard bristle for brushing their teeth as it causes more injury to the mucosa. Also they were advised to avoid coarse rough foods and very hot foods which can cause more injury to the mucosa.

A large percentage of the patients present with dysphagia upfront. They were advised for nasogastric tube insertion. For those without dysphagia, they were counseled about the possibility of developing dysphagia themselves due to mucositis and the need of doing a nasogastric insertion at such times. The patients were counseled on the importance of taking a good amount of nutrition as the exposure to radiation as well as chemotherapy means they need extra the anount of what they usually have. they were encouraged to take nutrinionally rich local foods including dairy products and fruits, eggs etc.

They were also advised to take at least 1.5-2 litres of water per day in regular intervals. All the patients were given protein supplements which were available in the department. Also if there was a need patients were given parenteral nutrition the form of

intravenous fluids and albumin infusions for short courses. The weights of patients were monitored regularly to see for any drastic change in the weight.

Patients were also counseled on the importance of the need of physical activity during the course of the treatment. Not strenuous physical activity, but moderate activity like a walk around the campus. Studies has shown that some form of physical activity during the course of treatment reduces the incidences of fatigue and also improves the quality of life and the psychological state of the patient.

Patients and their attenders were counseled about the importance of sticking to the treatment schedule and to avoid any treatment breaks unless otherwise indicated due to the development of side effects.

For those patients that had their homes nearby the hospital, they were encouraged to get their radiation daily from their homes as out-patients. They were admitted on their chemo days and then discharged after chemotherapy. They were monitored everyday when they came for radiation for signs and symptoms of radiation and chemotherapy.

TREATMENT PROTOCOL

30 patients of locally advanced squamous cell carcinoma of the head and neck enrolled in the study underwent the full pre-treatment work up and preparation. They were then started on concurrent chemoradiation using weekly cisplatin and daily tablet Gefitinib.

RADIATION THERAPY:

Patients were treated using theratron phoenix telecobalt machine with conventional 2D planning. They were treated using bilateral opposed fields which included the primary and the nodes. The patients were treated with conventional 2 Gy per fraction 5 fractions per week to a total dose of 66 Gy. At 40 Gy the posterior border was shifted anteriorly so as to avoid the spinal cord. The planned duration of the treatment was six and half weeks.

CHEMOTHERAPY

Patients were started on chemotherapy from day 1 of radiation. Injection Cisplatin 30mg/m^2 diluted in 500ml of Normal Saline was infused over 2 hours after premedications. Radiation was started within one hour of completion of chemotherapy. Patients received the subsequent cycles of chemotherapy at one week intervals.

Patients also received tablet Gefitinib 250mg once daily before Radiation. Patients were advised to take the tablets about 4 hours before the start of RT. The peak plasma level of Gefitinib is reached by 3-7 hours of oral intake.

PREMEDICATION

Patients were hydrated with 1L of NS before the start of chemotherapy along with following premedications.

Inj. Ondansetron 8 mg IV.

Inj. Dexamethasone 8mg IV.

Inj. Ranitidine 50 mg IV.

Inj. Chlorpheniramine 4mg IV.

Injection Cisplatin 30mg/m^2 mixed in 1 pint of NS was infused over 2 hours after which patients received pint of NS.

ASSESSMENT DURING CHEMORADIATION:

Toxicity Assessment:

The patients were examined everyday to see for any toxicities like mucositis, skin reactions, dysphagia, laryngitis, xerostomia. The findings were recorded and graded according to the RTOG acute toxicity criteria. Other effects of chemotherapy like nausea,

vomiting, diarrhea, skin rash were also looked for and graded. Blood tests were done every week before the initiation of chemotherapy and then if there was any abnormality like anemia or leucopenia, they were corrected by blood transfusions and G-CSF injections. For any abnormalities in the renal and liver functions, opinions from the specialist like nephrologist were obtained.

RESPONSE EVALUATION:

Clinical evaluation and imging by using contrast enhanced CT were done at sfter 6 weeks of completion of ChemoRT for response assessment.

Response to treatment was described based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1 version) Criteria.

- **COMPLETE RESPONSE**: Disappearance of all target lesions; malignant nodes <10 mm.
- **PARTIAL RESPONSE:** At least 30% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study
- **STABLE DISEASE**: Neither partial response nor progressive disease criteria are met, in a minimum time set by the protocol.

- **PROGRESSIVE DISEASE:** At least 20% increase in the sum of the diameter, with a minimum absolute increase of 5 mm, taking as reference the smallest sum in the study or appearance of new lesions.

FOLLOW UP

- The patients were advised to come after 6 weeks for response assessment after the completion of chemoradiation or to review SOS if they developed any significant problems in between.

- After the intial response assessment patients were kept on monthly follow up as per our institution protocol.

- They were advised continued abstinence from the use of tobacco and alcohol, to keep good oral hygiene.

- Other complaints and symptoms were dealt with as necessary.

STATISTICAL ANALYSIS:

All the results were compiled and analysed and expressed in terms of percentage. This is a single arm study with a sample size of 30, hence the statistical significance of the study cannot be commented upon.

RESULT AND ANALYSIS

All of the 30 patients that were included in the study completed the full course of treatment and were available for analysis. The following results were compiled.

PATIENT CHARACTERISTICS

GENDER

As expected, males were more as compared to the females. This reflects the more prevalence of risk factors of the use of tobacco and alcohol in the male population as compared to the female counterpart. **Fig 2**

Table no: 1, GENDER DISTRIBUTION OF THE STUDY POPULATION

Sex	No. Of patients	Percentage
Male	25	83.3%
Female	5	16.7%

AGE DISTRIBUTION:

Almost half of the patients were in the 51-60 years age group (46.66%). The percentage of patients in the younger age group is also high. The oldest patient included in the study was 68 years old. The youngest was 32years. Both were males associated with the use of tobacco. **Fig 3**

Table No-2: Age Distribution Of The Study Population

Age Group	Number	Percentage
31- 40yrs	4	13.33%
41 -50yrs	8	26.66%
51-60yrs	14	46.66%
61-70yrs	4	13.33%

PERSONAL HABITS

Majority of the patients had history (86.66%) of use of tobacco in its various forms. 14 of them had concomitant use of alcohol (46.66%). Only 4 of them did not give any history of use of tobacco or alcohol, all of whom were females. **Fig 4**

Table no: 3

Habits	No.of patients	Percentage
Tobacco (Smoking)	21	70%
Tobacco (Smokeless)	12	40%
Alcohol	14	46.66%
None	4	13%

SYMPTOMS AND SIGNS

Majority of the patients presented with the complaint of pain and a equal number with the complaint of dysphagia. 15 (53.33%) patients presented with the complaint of neck swelling.

Table no: 4, symptoms/signs

Presenting symptoms/signs	Number	Percentage
Pain	18	60%
Ulcer/ Growth	6	20%
Dysphagia	17	56.66%
Odynophagia	9	30%
Neck swelling	16	53.33%
Voice change	5	16.66%

DURATION OF SYMPTOMS ACCORDING TO SITE WISE

Mean duration of the presenting symptoms were similar amongst the different subsites. Longest duration of symptom was a laryngeal cancer where patient presented with a history of hoarseness of voice for 6 months associated with progressive dysphagia for the past 2 months

Table 5.

Site	Mean Duration(in months)
Oral cavity	3
Oropharynx	3.3
Larynx	3.6
Hypopharynx	3.1

PERFORMANCE STATUS

Most of the patients had a ECOG performance status of 2 at the time of presentation. **Fig 6**

Table No:6, ECOG performance status

ECOG	No.of patients	Percentage
ECOG 0	8	26.7%
ECOG 1	17	56.6%
ECOG 2	5	16.6%

PRIMARY SITE

Oropharynx and hypopharynx were the most common sites for primary. Each making up 30% of the study population. **Fig 7**

Table no:7

Primary site	Number	Percentage
Oral cavity	6	20%
Oropharynx	9	30%
Hypopharynx	9	30%
Larynx	6	20%

Comparing the various subsites, the most common were in the post cricoids region, followed by the supraglottis, the posterior 1/3 tongue and the tonsil.

Table No: 8, subsite analysis

Subsite	Number	Percentage
Tongue	4	20%
Floor of mouth	1	3.33%
Buccal mucosa	1	3.33%
Posterior 1/3 tongue	5	16.66%
Tonsil	4	13.33%
Post cricoid	2	6.66%
Pyriform sinus	7	23.33%
Supraglottis	6	20%

TUMOR STAGE

Most of the patients had a T4 (56.66%) disease at the time if presentation. **Fig 8**

Table no:9, Tumor stage

T stage	Number	Percentage
T2	1	3.33%
T3	12	40%
T4	17	56.66%

NODAL STAGE

N2 was the most common nodal presentation (70%). 10% of the patients did not have any clinically significant nodes at the time of presentation. **Fig 9**

Table no: 10, Nodal stage

Nodal stage	Number	Percentage
N0	3	10%
N1	6	20%
N2	21	70%

STAGE GROUPING OF THE STUDY SAMPLE

Stage IVA was the most common stage at the time of presentation (80%) **fig 10**

Table no: 11, stage grouping

Stage grouping	Number	Percentage
STAGE III	6	20%
STAGE IV A	24	80%

HISTOLOGICAL DIFFERENTIATION

Majority of the tumors were moderately differentiated (60%) **Fig 11**

Table No:12, Histological differentiation

Histological differentiation	Number	Percentage
Well differentiation	4	13.33%
Moderately differentiated	18	60%
Poorly differentiated	8	26.66%

TREATMENT RESULTS

All 30 patients that were initially enrolled in the study were able to fully complete the treatment protocol. They were assessed clinically and by CT with contrast after 6 weeks of treatment for response evaluation and thendescribed as per the RECIST criteria.

RESPONSE RESULTS

Overall response rate was 100% of which 76.6% of the patients had complete response and 23.3% had partial response. There was no static response or progressive disease in the study.(**figure no:12**)

Table no:13, Response results

Response	Number	Percentage
Complete response	23	76.66%
Partial presponse	7	23.33%

SITE VS RESPONSE

Oropharynx, hypopharynx and laryngeal cancers had good response rates as compared to oral cavity cancers. **Fig 13**

Table no:14, Site Vs Response

Site	Complete Response	Partial response
Oralcavity	4(66.6%)	2(33.3%)
Oropharynx	7(77.8%)	2(22.2%)
Hypopharynx	7(77.8%)	2(22.2%)
Larynx	5(83.3%)	1(16.66%)

TUMOR STAGE VS RESPONSE

T3 diseases had a 83.3% complete response rate as compared to T4 lesions which had 70.6% complete response rates. **Fig 14**

Table no: 15, Tumor Stage Vs Response

Tumor stage	Complete Response	Partial response
T2	1(100%)	0
T3	10(83.3%)	2(16.66%)
T4	12(70.6%)	5(29.4%)

NODAL STAGE VS RESPONSE

All N1 and N2A diseases had 100% complete response. The complete response rates for N2B and N2C diseases were 85.75% and 60% respectively **Fig 15**

Table no:16, Nodal Stage Vs Response

Nodal stage	Complete Response	Partial response
NO	3(100%)	0
N1	6(100%)	0
N2a	4(100%)	0
N2b	6(85.7)	1(14.3%)
N2c	6(60%)	4(40%)

HISTOLOGICAL DIFFERENTIATION VS RESPONSE

The response rates correlated with the histological differentiation with poorly and moderately differentiated tumors having higher rates of complete response as compared to the well differentiated primaries. **Fig 16**

Table no: 17, Histological differentiation Vs response.

Histologic differentiation	Complete response	Partial response
Well differentiated	2(50%)	2(50%)
Moderately differentiated	14(77.8%)	4(22.2%)
Poorly differentiated	7(87.5%)	1(12.5%)

PERFORMANCE STATUS VS RESPONSE

The response rates were similar between patients having ECOG performance status of 0 or 1 OR 2. **Fig 17**

Table no: 18, ECOG Vs Response

ECOG	Complete response	Partial response
0	6(75%)	2(25%)
1	13(76.5%)	4(23.5%)
2	4(80%)	1(20%)

PRIMARY AND NODAL SITES – DIFFERENTIAL RESPONSE

In this study the complete response rate in the primary site was 76.6% whereas in that of the nodal region was 83.3%.

AGE VS RESPONSE

The response rates across the age groups were similar in this study **Fig18**

Table no: 19, Age Vs Response

Age group	Complete response	Partial response
31-40Yrs	3(75%)	1(25%)
41-50Yrs	6(75%)	2(25%)
51-60Yrs	14(78.5%)	3(21.4%)
61-70Yrs	3(75%)	1(25%)

STAGE VS RESPONSE

Stage III patients had better complete response rates (86.66%) as compared with stage IVA disease (75%) **fig 19**

Table no :20, Stage Vs Response

Stage	Complete response	Partial response
STAGE III	5(83.33%)	1(16.66%)
STAGE IV	18(75%)	6(25%)

TREATMENT BREAK VS RESPONSE

Prolongation of the total treatment time adversely effects the treatment outcome and survival. So it is important that that the treatment gets completed without any break.

In this study group 56.6% (17) of the patients had completed the treatment without any break. The main cause of treatment break was mucositis. In this study those who had a longer duration of break in the treatment had more treatment failure rates as compared with those who completed the treatment with no breaks or had minimal breaks of 1-5 days. **Fig 20**

Table no: 21, Treatment break Vs Response

Treatment break	Number	Complete response	Partial response
No break	17	14(82.3%)	3(17.6%)
1-5 Days	8	6(75%)	2(25%)
> 6 Days	5	3(60%)	2(40%)

TREATMENT RELATED ACUTE TOXICITIES

MUCOSITIS

In this study all patients developed some form of mucositis. As expected there was high incidence of mucositis in this study. Overall 70% had grade 1or 2 mucositis and 30% had grade 3 or 4 mucositis requiring treatment breaks. Around 43% had grade 2 mucositis and 26% had grade 3 mucositis. Only one patient had grade 4 mucositis.

SKIN REACTION

All patients had some form of skin reaction however there was no grade 3 or 4 reactions in this study. 80% had grade 1 reaction and the remaining had grade 2.

SALIVARY GLAND /XEROSTOMIA

The salivary glands has a comparatively low tolerance dose and is reflected in the results of this study. 73.3% of the patients had grade 1 reraction and the remaining had grade 2. There were no grade 4 reactions in this study.

PHARYNGITIS AND DYSPHAGIA

During the course of the treatment all patients had some form of dysphagia. 33% had grade 1 dysphagia, around 36% had grade 2 and 30% had grade 3 dysphagia.

LARYNGITIS

Around 33% had grade 1 laryngitis, 46% had grade 2 and the remaining had grade 3 laryngitis.

Table no:22, Acute toxicity Fig 21

Acute Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin reactions	0	23 (76.66%)	5 (16.66%)	2 (6.66%)	0
Mucositis	0	8 (26.6%)	13 (43.3%)	8 (26.6%)	1 (3%)
Salivary gland	0	22 (73.3%)	8 (26.7%)	__	0
Pharyngitis/ Dysphagia	0	10 (33.33%)	11 (36.67%)	9 (30%)	0
Laryngitis	0	10 (33.33%)	14 (46.67%)	6 (20%)	0

SYSTEMIC TOXICITY

NAUSEA

73.3% of the patients had grade 1 nausea. Only 1 person had grade 3 nausea.

VOMITING

76.6% of patients had vomiting commonly after the infusion of chemotherapy all of which responded to the routine anti-emetic measures. The remaining had grade 2 nausea. There was no episode of severe vomiting in any of the patients.

DIARRHOEA

4 patients had grade 1 diarrhea and only 1 patient had grade 2 diarrhoea. There were no grade 3 or 4 toxicities

GEFITINIB RELATED SKIN RASH

Only one patient developed the classical skin rash associated with the use of gefitinib. It was a grade 1 skin reaction and did not necessitate the need for suspending the drug. It developed during the 3rd week of treatment and resolved with symptomatic treatment.

Table no: 23,Systemic toxicity Fig 22

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	22 (73.3%)	7 (23.3%)	1 (3.33%)	0
Vomitting	23 (76.6%)	7 (23.3%)	0	0
Diahorrea	4 (13.3%)	1 (3.33%)	0	0

HEMATOLOGICAL TOXICITY

ANAEMIA

The hemoglobin of all the patients were >11gm% before the start of treatment. 5 patients had hemoglobin below 11gm% and were corrected by transfusion before the start of treatment. During the course of treatment, 9 patients developed grade 1 anemia and 2 of them developed grade 2 anemia, which was corrected with blood transfusion.

Table no: 24, Anemia Fig 23

Anemia	Number	Percentage
GRADE 0	19	63.3%
GRADE 1	9	30%
GRADE 2	2	6.7%
GRADE 3	0	0
GRADE 4	0	0

LEUCOPENIA

Of the 30 patients, only two developed leucopenia grade 1. All the rest had total count> 4000/mm^2 throughtout the course of treatment. There were no episodes of febrile neutropenia or thrombocytopenia.

RENAL TOXICITY

The renal parameters of all the patients were normal throughout the course of treatment.

DISCUSSION

Squamous cell carcinoma of the head and neck is one of the most prevalent cancers in India and has a high social and economic impact. Majority of the patients present in the locally advanced stage where surgical resection is either not possible or is associated with a lot of morbidity. Historically such patients were treated with local RT alone where the local control rates were between 50-70% and the 5 year survival was a dismal 10-20%[20].

There was a definite rationale for the combined use of chemotherapy and radiation in locally advanced head and neck cancer. Chemotherapy sensitizes tumors to radiotherapy by inhibiting tumor repopulation, it preferentially kills the hypoxic cells, inhibiting the repair of sublethal damage caused by radiation, it sterilizes the micrometastatic disease outside the radiation fields and also decreases the tumor mass which leads to improved blood supply and reoxygenation thus potentiating the effect of radiation. Fractionated radiotherapy, sensitizes tumors to chemotherapy by inhibiting the repair caused by chemotherapy. It also decreases the size of the tumor causing improved blood

supply to the tumor such that the chemo can more easily reach the tumor cells leading to more cytotoxic effect.

Several trials investigating the feasibility as well the improvement of outcomes by using chemotherapy along with radiation were performed. In most of the trials cisplatin was the mainstay of chemotherapy and it was used alone or in combination with some other agents. The expected theoretical advantage of adding another cytotoxic agent in the form of chemotherapy to that of radiation was clearly demonstrated in these trials and was confirmed by a number of meta-analysis.

Many meta−analyses have been conducted to show whether chemo−radiotherapy association is better than radiotherapy alone as concerns LRC or survival[21-23]. Among these meta-analyses the most well known and important one is the Meta- Analysis on Chemotherapy on Head and Neck cancer (MACH-NC) published by Pignon et al[8]. It showed that adding chemotherapy to radiation had the following advantages in locally advanced cancer of the head and neck:

1) The use of chemotherapy increased the overall survival at 5 years by 5% irrespective of the timing of association

2) The concurrent use of chemotherapy with radiation improved the overall survival by 8%

3) The use of neoadjuvant chemotherapy followed by radiation alone is less effective as compared to concurrent chemoradiation

4) The use of cisplatin as the chemotherapy has evident benefit

5) The use of combination chemotherapy does not seem to provide added advantage over the use of single agent.

6) And as the age of the patient increase over 70, the benefit of adding chemotherapy is less evident.

As of now the standard of care for all those locally advanced unresectable head and neck cancer is concurrent chemoradiation with a radiation dose of upto 70 Gy and three weekly cisplatin of 80-100mg/m^2. However the three weekly regimen is associated with a number of toxicities and poor compliance. Literature wise evidence exists that the weekly regimen of cisplatin is as efficacious as the three weekly regimen as long as a minimum threshold cumulative dose of 200mg/m^2 is achieved. This comes with a significant lesser toxicity in the weekly arm. In a study

conducted in our department, the weekly regimen was as efficacious as the three weekly regimen with lower toxicities.

CISPLATIN WITH RADIATION	COMPLETE RESPONSE RATE IN %	PARTIAL RESPONSE RATE IN %
THREE WEEKLY	64	36
WEEKLY	62	38

The use of concurrent chemoradiation in locally advanced setting is now the standard of treatment worldwide. With this treatment the overall survival has increased to about 50-60% with the best of treatment. However even with the use of a variety of treatment approaches the overall survival has failed to improve significantly. Several trials are going on for the development of new drugs and that may help improve the overall survival.

One of these fields is that of molecular biology. It is said that to defeat an enemy one must know the enemy. Better the knowledge easier will it be to fight. The same principle can be applied to the field of oncology also. From the knowledge that all cancers are not the same but of different histology and morphology, and has a different behavior to knowing that there are variations within the same histology our knowledge has now expanded to include the

domain of molecular biology. A better understanding of the pathogenesis of cancer the various mechanisms, growth factors and pathways that are involved and knowledge of proteins involved in these activities has allowed for their targeting by use of various drugs. They offer a very attractive prospect where the tumor cells can be targeted specifically instead of the mass general cytotoxicity offered by the other chemotherapies. Thus, decreasing the toxicity of treatment and also improving the outcome.

The EGFR pathway provides a promising pathway for targeting as almost 90% of the head and neck squamous cell carcinoma over express this receptor. It plays a pivotal role in tumor growth, invasion, angiogenesis and metastasis. Preclinical trials have shown that the addition of a anti-EGFR has a synergistic effect with radiation. Cetuximab (Erbitux) is a monoclonal antibody specific against the EGFR receptor. In a landmark trial by Bonner et al it was clearly demonstrated that the concomitant use of RT plus Cetuximab significantly improved the Locoregional Control Rate, the Disease free Survival and overall survival in patients with locally advanced head and neck squamous cell carcinoma[D1]. Since then a number of trials have been done researching the benefit of

adding targeted therapy along the standard chemoradiation protocol.

The other group of drugs against EGFR are the TKIs like Gefitinib and Erlotinib. These drugs are even less toxic than the monoclonal antibodies. They have proven their worth in lung cancer where recent trials have shown that the use of TKIs significantly improves the progression free survival and the overall survival in specific subset of patients having the EGFR mutation.

A number of trials have been done in head and neck squamous cell carcinoma using these TKIs with the believe that their use will have a significant impact on the treatment outcome considering the high expression of EGFR in these patients. These trials have been done in the recurrent and metastatic setting as well as in those with newly diagnosed disease. However the results have been mixed and the benefit not as clear cut as that seen in lung cancer. Potential mechanisms for lack of response to EGFR inhibition in HNSCC include constitutive activation of signaling pathways independent of EGFR, as well as genetic aberrations causing dysregulation of the cell cycle. EGFR-directed therapy may be optimized by identifying and selecting those HNSCC patients most likely to benefit from EGFR inhibition. Resistance to

EGFR inhibition may be circumvented by combination therapy employing EGFR inhibitors together with other treatment modalities **(Kalyankrishna & Grandis 2006)[24].**

In several phase II trials, the use of gefitinib in combination with the standard chemoradiotherapy has shown to improve the immediate response rates and the locoregional control rates. But the impact of the addition of Gefitinib on the overall survival is yet to be assessed in a large scale randomized trial. Several trials are ongoing which will hopefully provide a definite answer for this question in the near future.

Keeping the various studies and findings in mind, we wanted to evaluate whether the addition of Gefitinib could improve he treatment outcome in our patients with locally advanced head and neck cancer.

In this present study the overall response rate (CR+PR) was 100% with 76% of the patients achieving a compete response and the remaining had partial response. There was no significant association of the response to therapy when compared with the gender of the patient, the age of diagnosis, performance status of the patient.

In this study, primary tumors in the oropahrynx, hypopharynx and the larynx had a better response to treatment as compared to those in the oral cavity. This may be due to the fact that most of the oral cavity tumors were well differentiated and had a poor response to treatment. This also corroborated with the finding where poorly differentiated tumors had better treatment response rates as compared with the well differentiated histologies.

Tumors with lesser volume of disease i.e. T3 diseases had better response rates as compared with the T4 diseases and the same findings were seen in the nodal disease where N1 and N2A tumors responded better than the N2B and 2C tumors. Also the response rates in the nodal region was better than that in the primary with 83% achieving a complete response in the nodal site as vompared to 76% in the primary.

Also those who had a break in the continuity of the treatment had a worse outcome as compared with those who had no breaks. Those who had no treatment break had complete response rates of 82%, those with less than5 days break ahd a CR of 75% and those who had more than 5 days of break had a CR of 60 %. This reflects the importance of completing the treatment without any break as

the problem of accelerated repopulation can lead to treatment failure.

Compared with the historical data and also the department data, the use of gefitinib along with chemoradiation resulted in better response rates with 76% of the patients achieving a complete response as compared to 64-65% in the historical and department data. But this finding is not statistically significant due to the small study population.

Even though all of the patients developed some form of acute toxicity to chemoradiation, the rates of grade 3 and 4 toxicities were low. Only 6% of the patients had grade 3 skin reaction and no grade 4 reactins. Also the rates of grade 3 and grade 4 mucositis were 26% and 3% respectively. The incidence of grade 3 pharyngitis and laryngitis were 30% and 20% respectively. There were no grade 4 reactions.

Other systemic toxicities like nausea, vomiting, diarrhea were also seen in the patients but all were manageable with routine anti emetic measures. Only 1 patient had grade 3 nausea. Non of the patients had grade 3 diarrhoea or vomiting.

The hematogical toxicity was also minimal with no incidence of grade 3 or 4 toxicity. 6% of the patients had grade 2 anemia which was corrected with blood transfusion. There was no incidence of any febrile neutropenia or thrombocytopenia in the patients. There was no incidence of any renal toxicity or liver toxicity in any of the patients.

Only one patient developed the classical rash that is associated with the use of Gefitinib. It was a grade 1 reaction and resolved by cponservative management alone. No treatment break was required.

In our study the addition of Gefitinib to concurrent chemoradiation was found to be well tolerated. Compared with the historical data in our department as well as the world literature the response rates to our treatment was better with higher percentage of the patients achieving a complete response. But the sample size is small and this finding even though encouraging is not statistically significant. The regimen also had a good compliance rate with a large proportion of the patients completing the treatment without any break or a minimal break.

The major limitations of this study included its small sample size and short follow−up period. It is known that most of the SCCHN over−express EGFR which adds to the rational of using Gefitinib in this disease. However, EGFR Expression study could not be done in all patients due to financial reasons as it involves considerable cost. So, a subgroup analysis with EGFR wild type, mutated or over−expression parameters was not possible. Larger multi−centric trials are needed to confirm and validate the encouraging results of our study before Gefitinib could be recommended in routine clinical practice along with concurrent cisplatin−based chemo−radiation which is the current standard of care in locally advanced SCCHN.

CONCLUSION

In conclusion, it can be stated that the problem of head and neck cancer continues to grow with the passing years and efforts to curb the disease has failed to make a significant impact on this problem. Hence more amount of patients are presenting with locally advanced cancers. In such patients the addition of Gefitinib to the standard concurrent chemoradiation protocol seems to be a good option showing a better response rates than the standard arm. The regimen is also well tolerated with a severe increase in the toxicity and patient compliance is good. But this study was done in a small study sample and faile to reach statistical significance. Larger trials are needed to validate these encouraging findings and to more clearly define the role of Gefitinib in the management of locally advanced head and neck cancer.

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FIG2. SEX DISTIBUTION

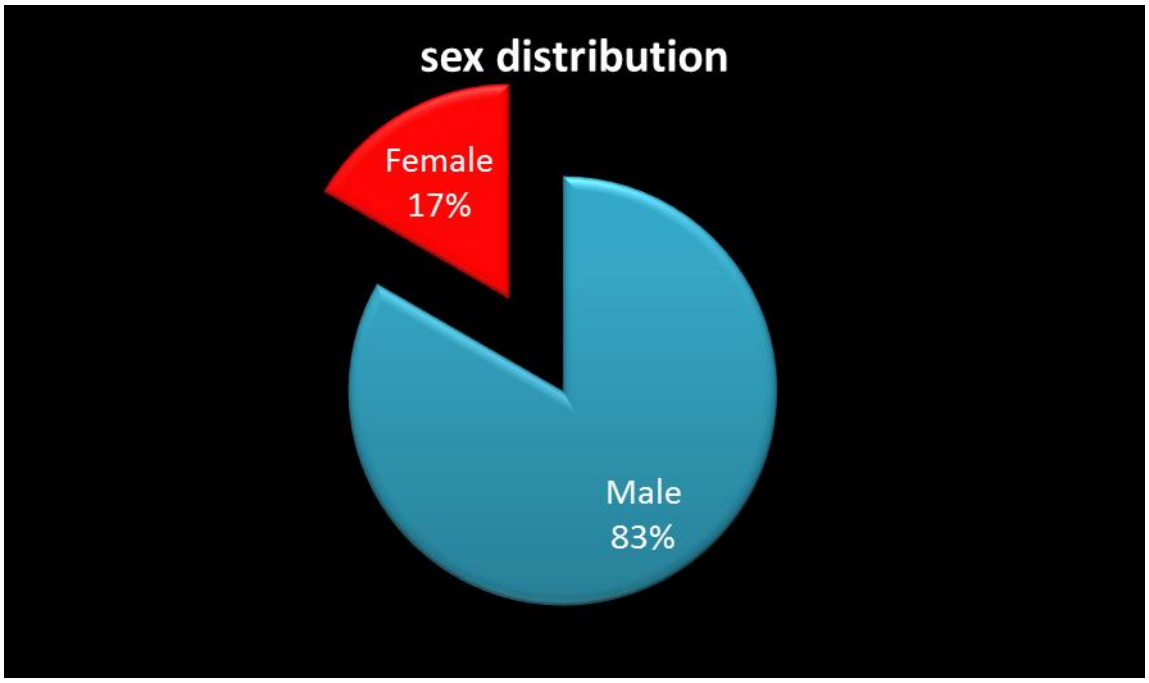


FIGURE 3. AGE DISTRIBUTION

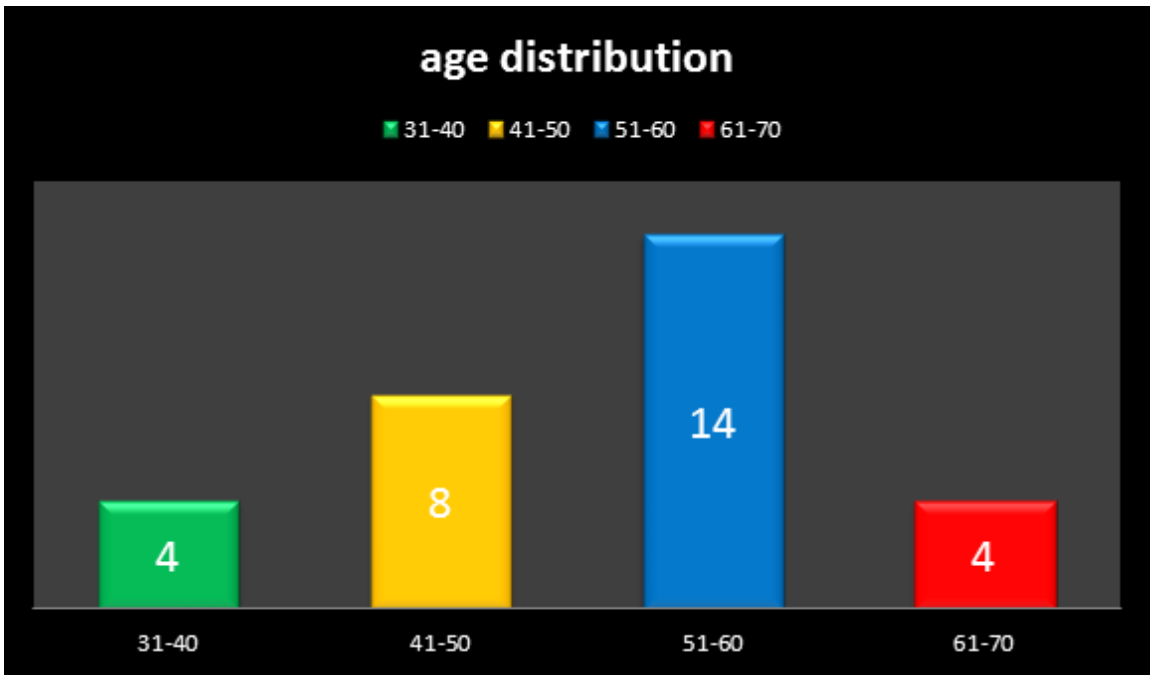


FIGURE 4 PERSONAL HABITS

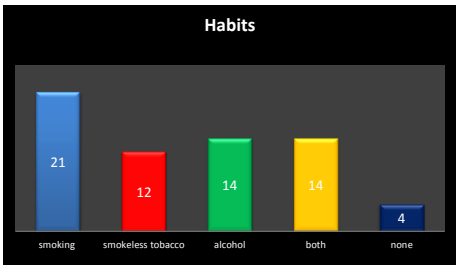


FIGURE 5 SIGNS AND SYMPTOMS

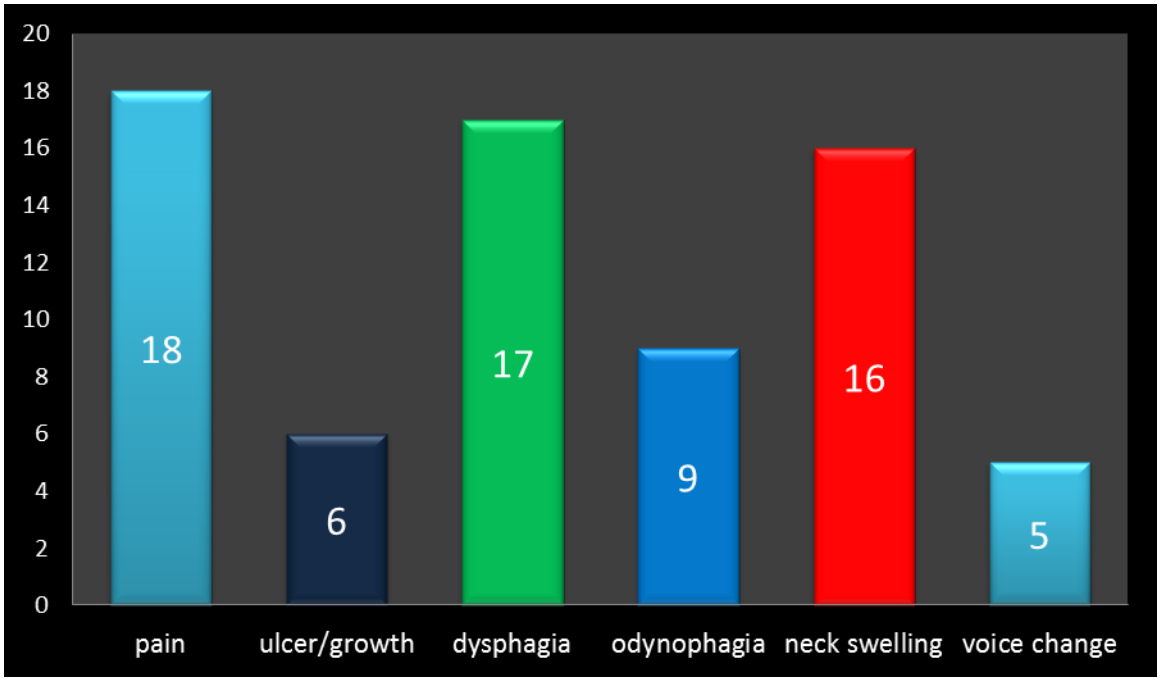


FIG 6 PERFORMANCE STATUS

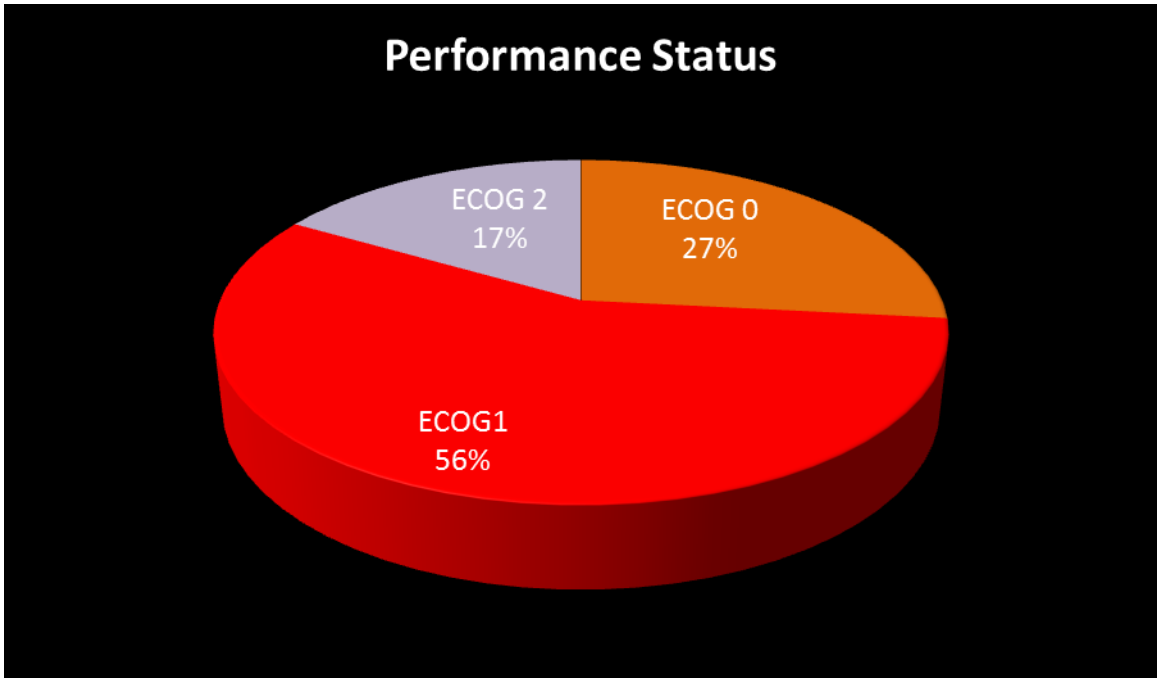


FIG 7 PRIMARY SITE

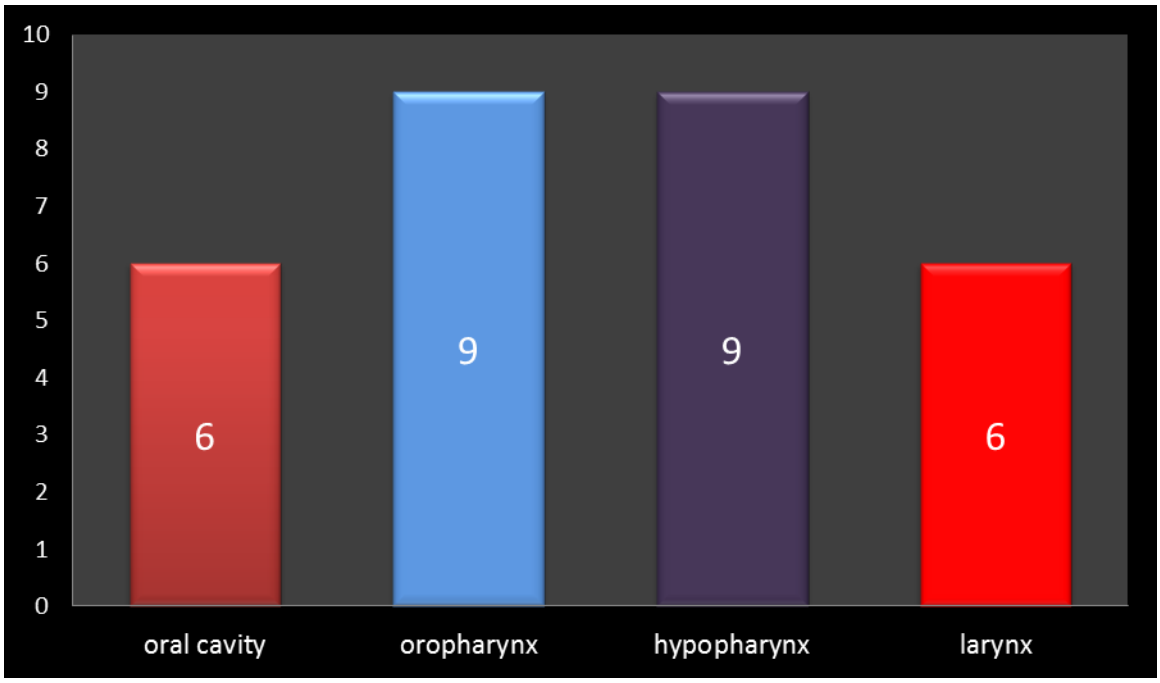


FIG 8 PRIMARY TUMOR STAGE

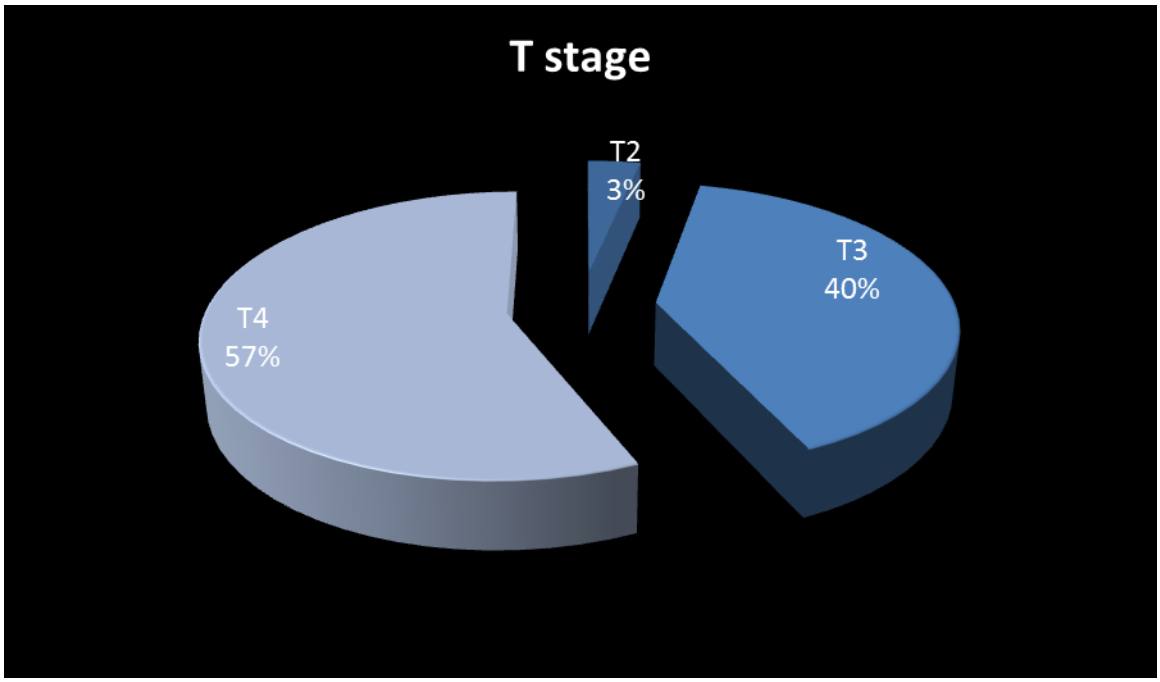


FIG 9 NODAL STAGE

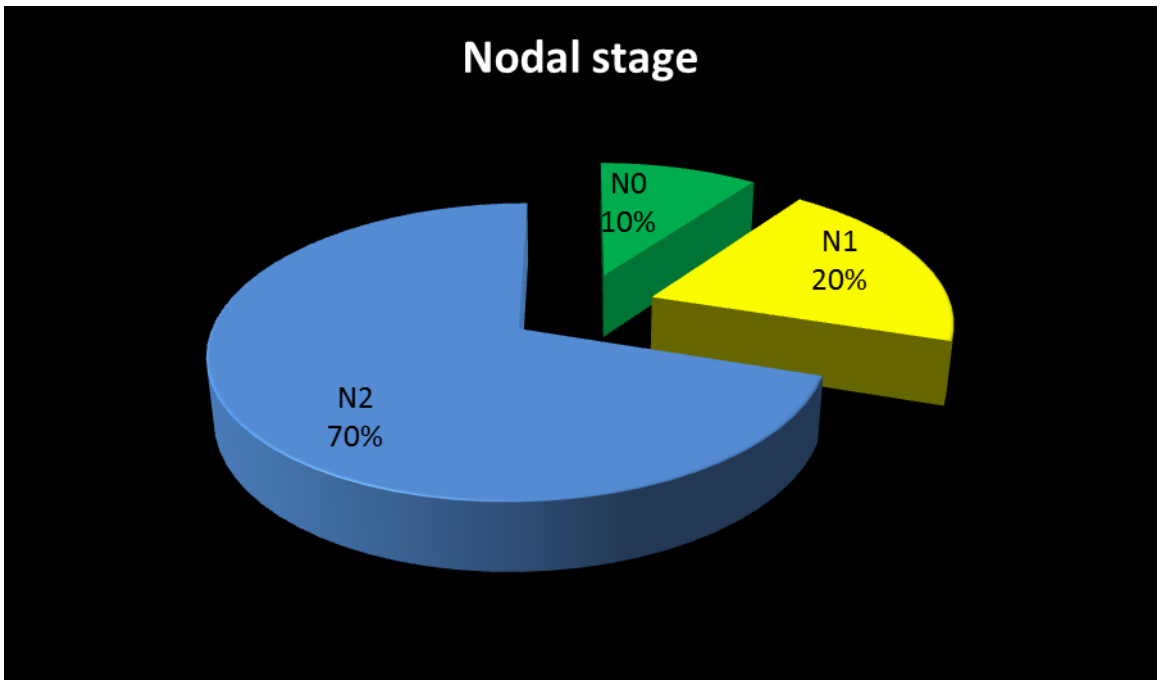


FIG 10 STAGE DISTRIBUTION

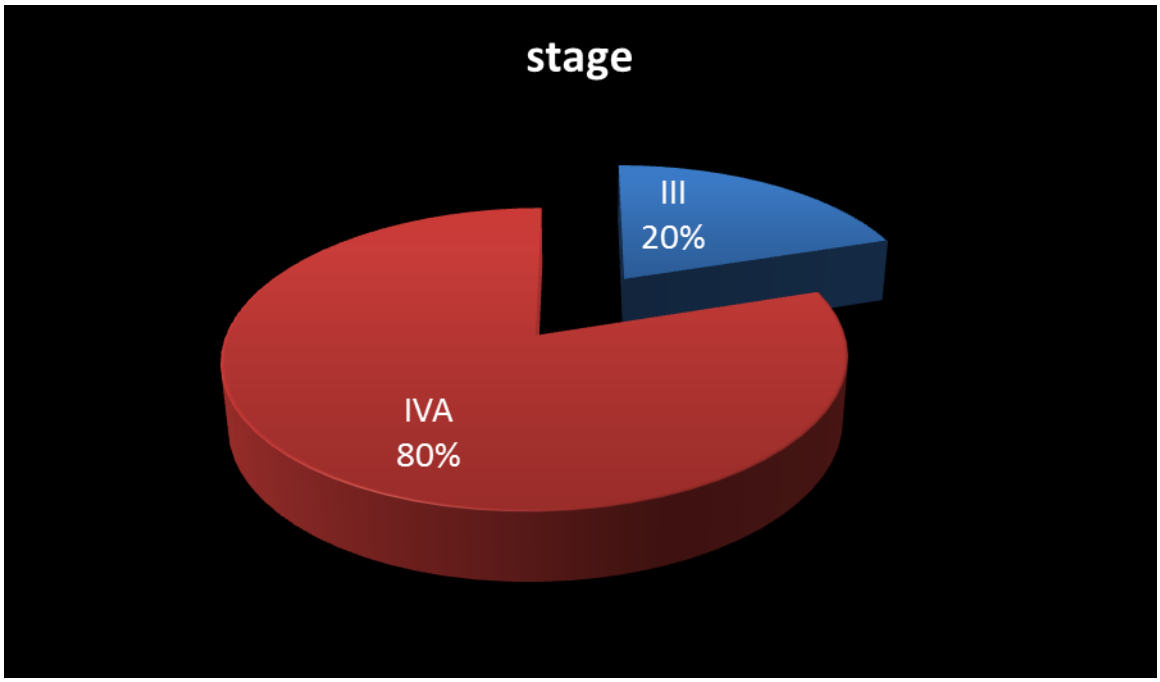


FIG 11 HISTOLOGICAL DIFFERENTIATION

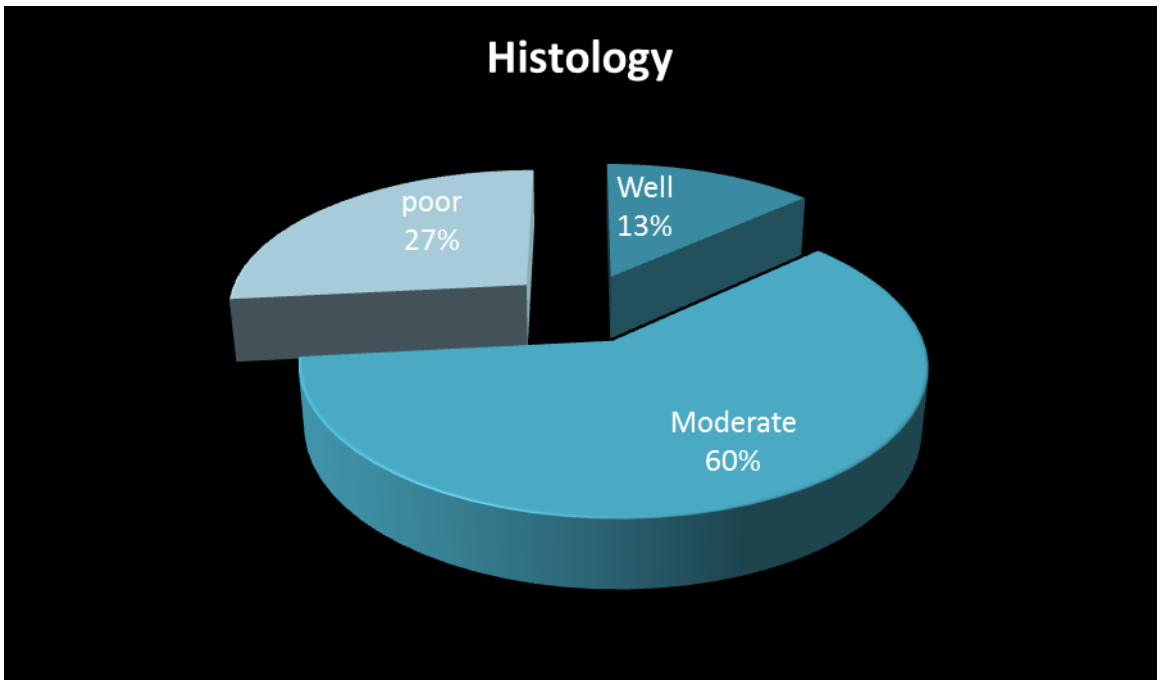


FIG 12 OVERALL RESPONSE RATES

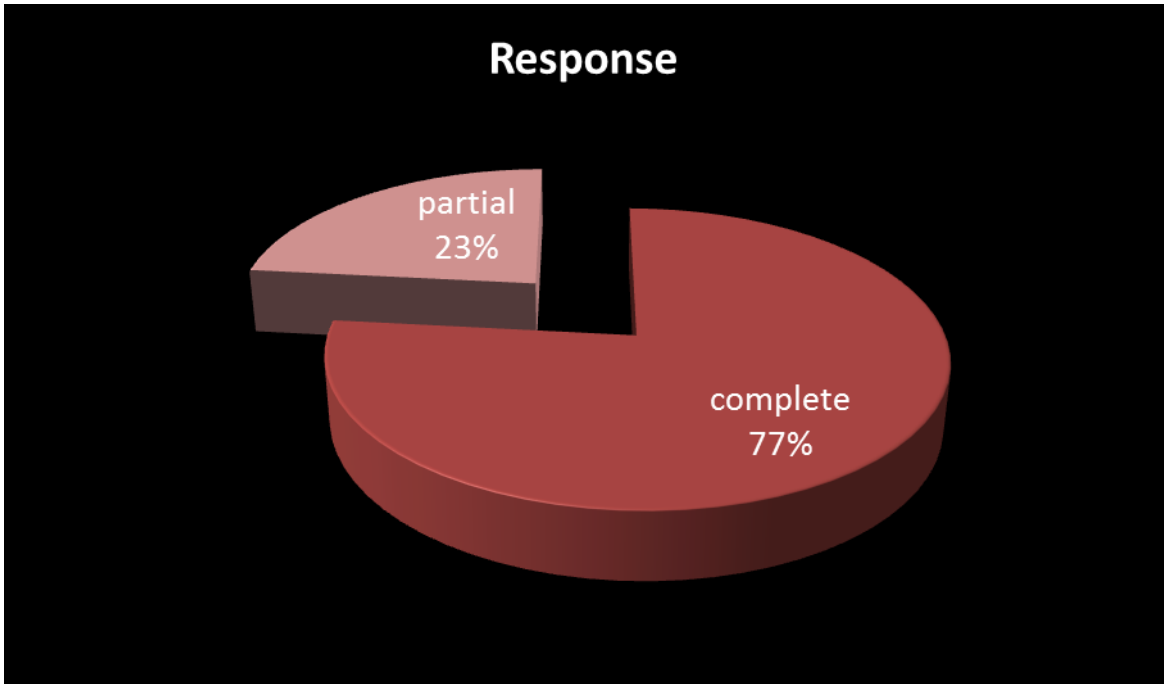


FIG 13 SITE VS RESPONSE

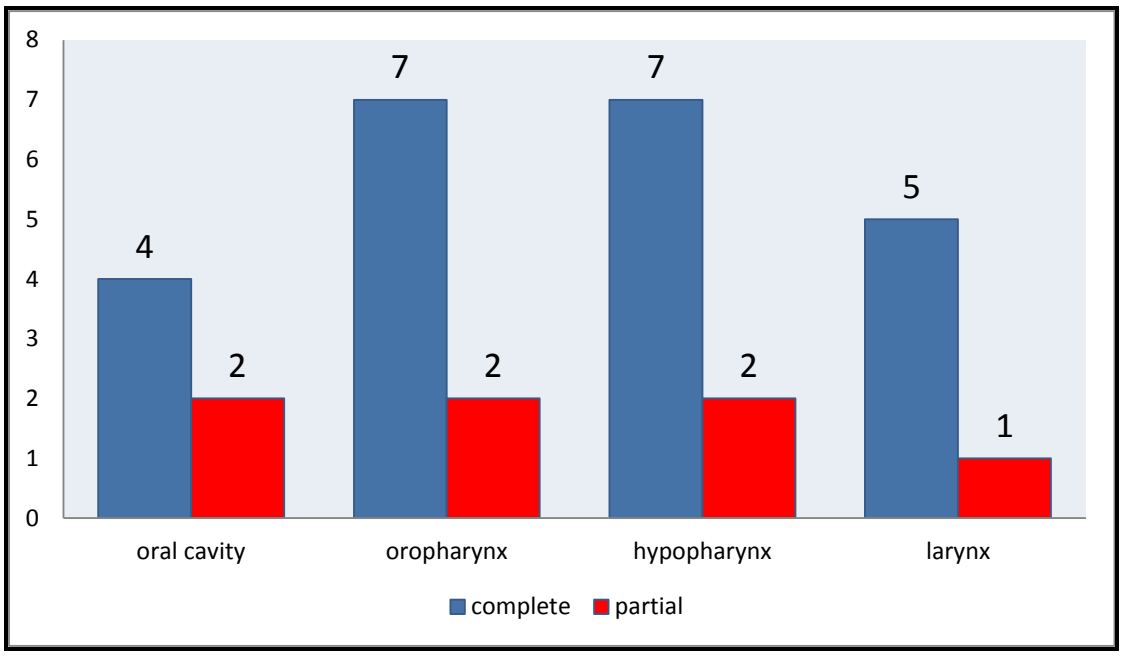


FIG 14 TUMOR STAGE VS RESPONSE

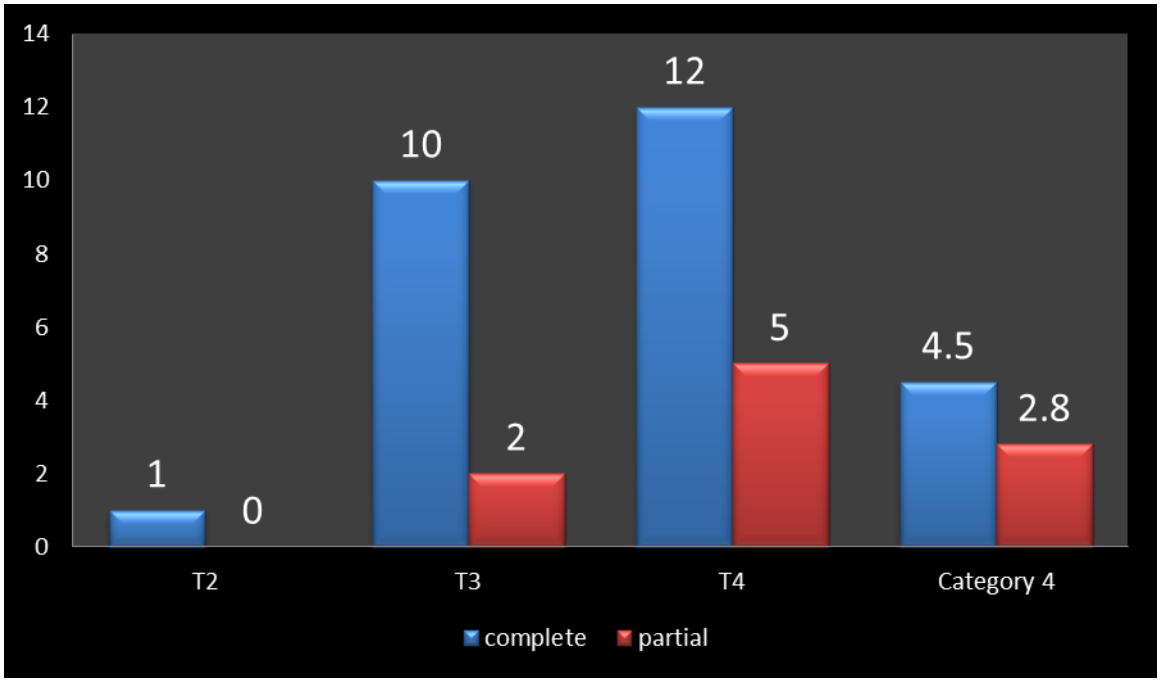


FIG 15 NODAL STAGE VS RESPONSE

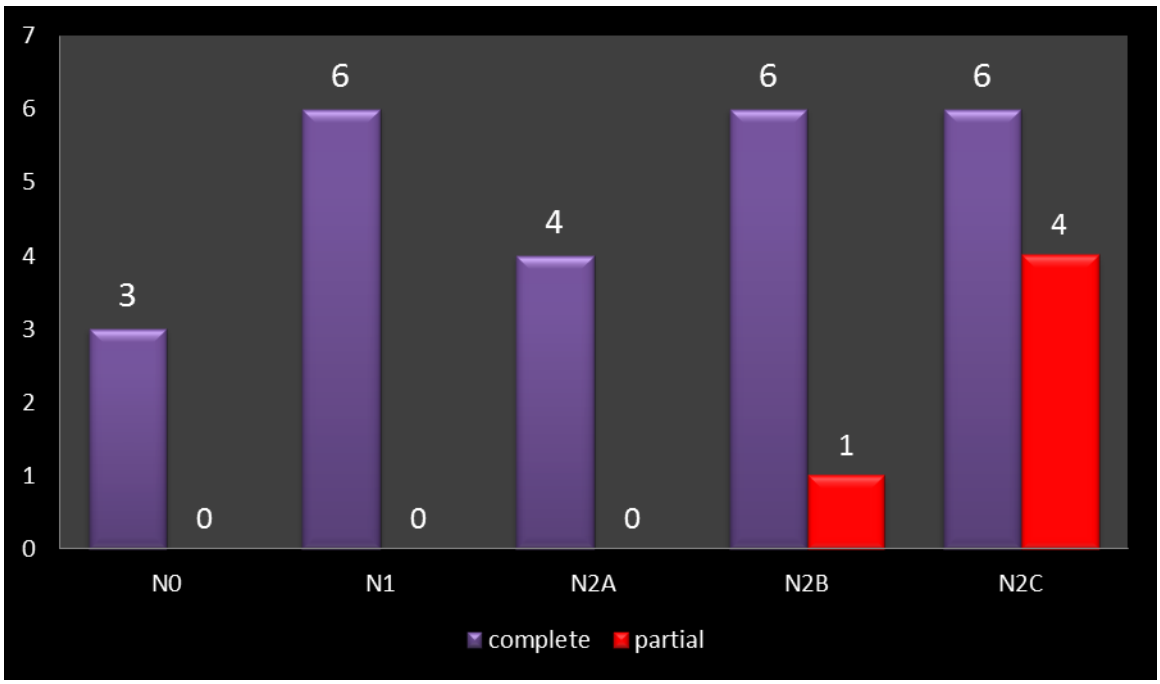


FIG 16 HISTOLOGY VS RESPONSE

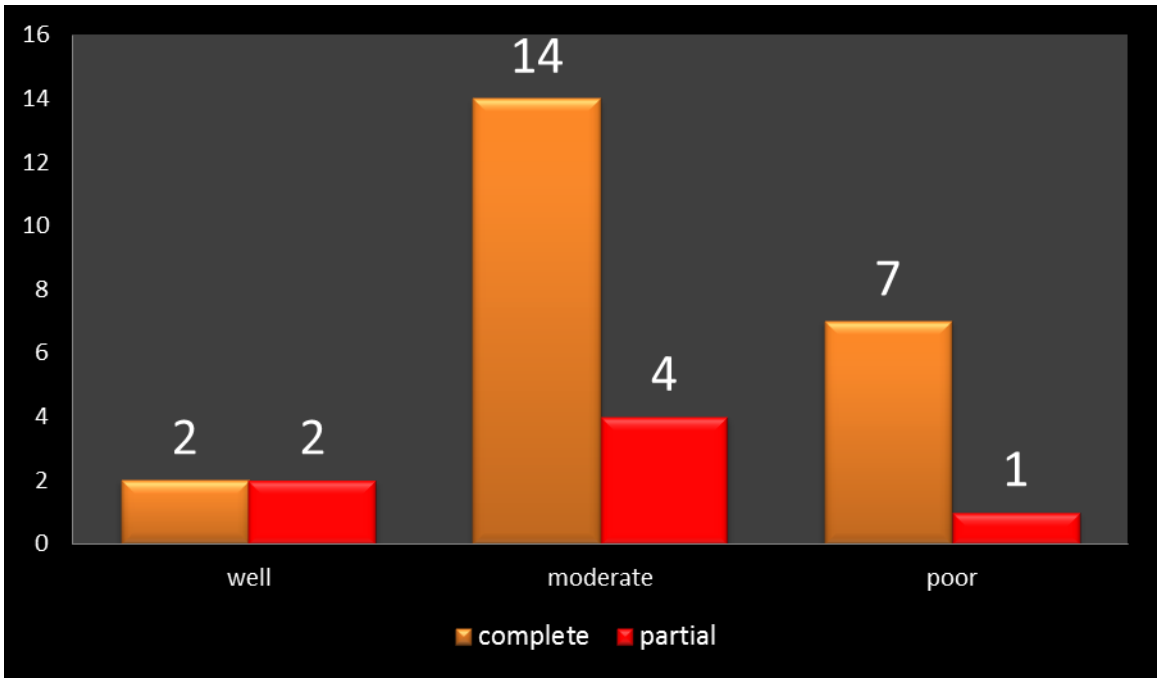


FIGURE 17 PERFORMANCE STATUS VS RESPONSE

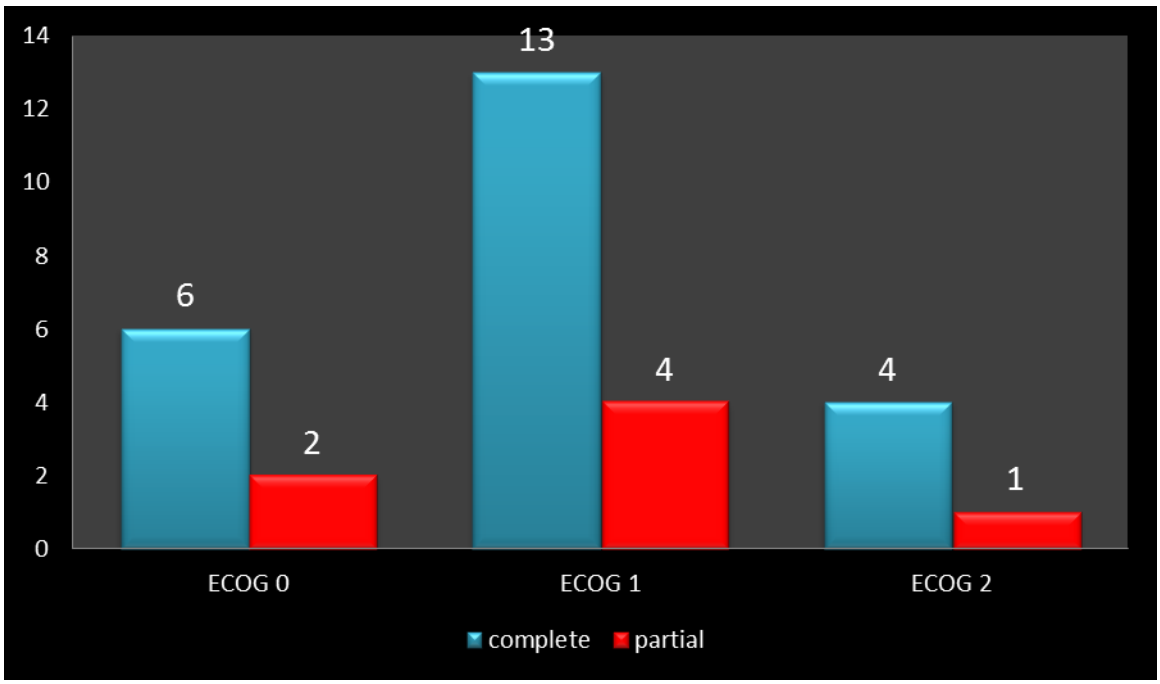


FIGURE 18 AGE VS RESPONSE

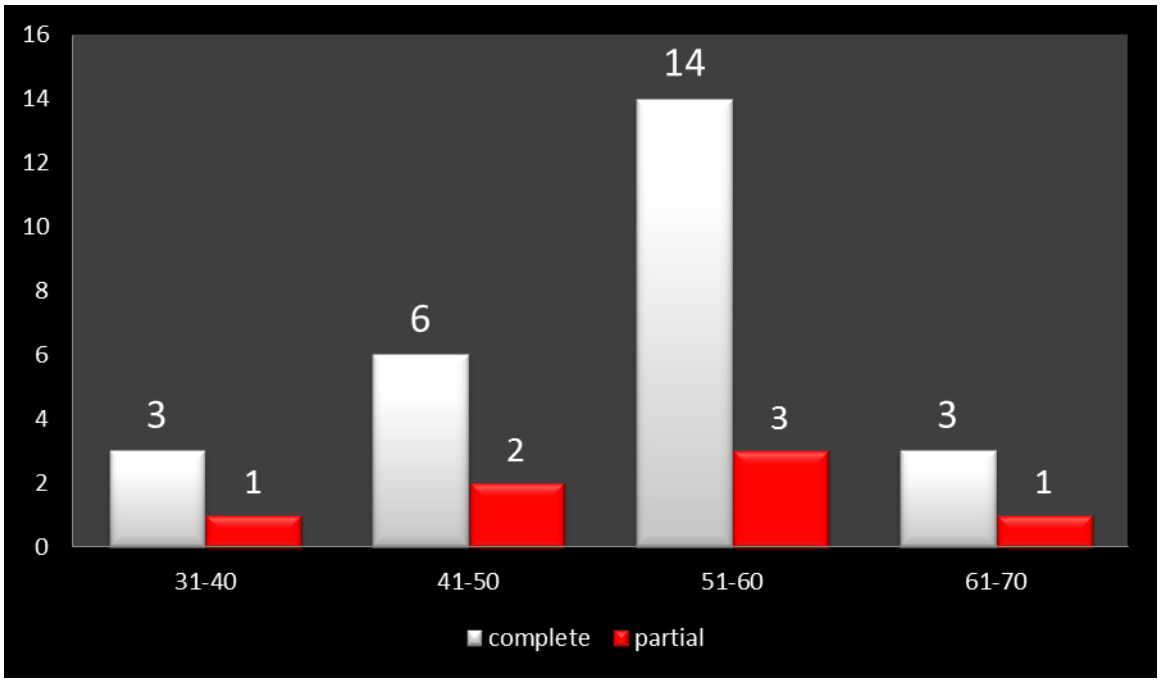


FIG 19 STAGE VS RESPONSE

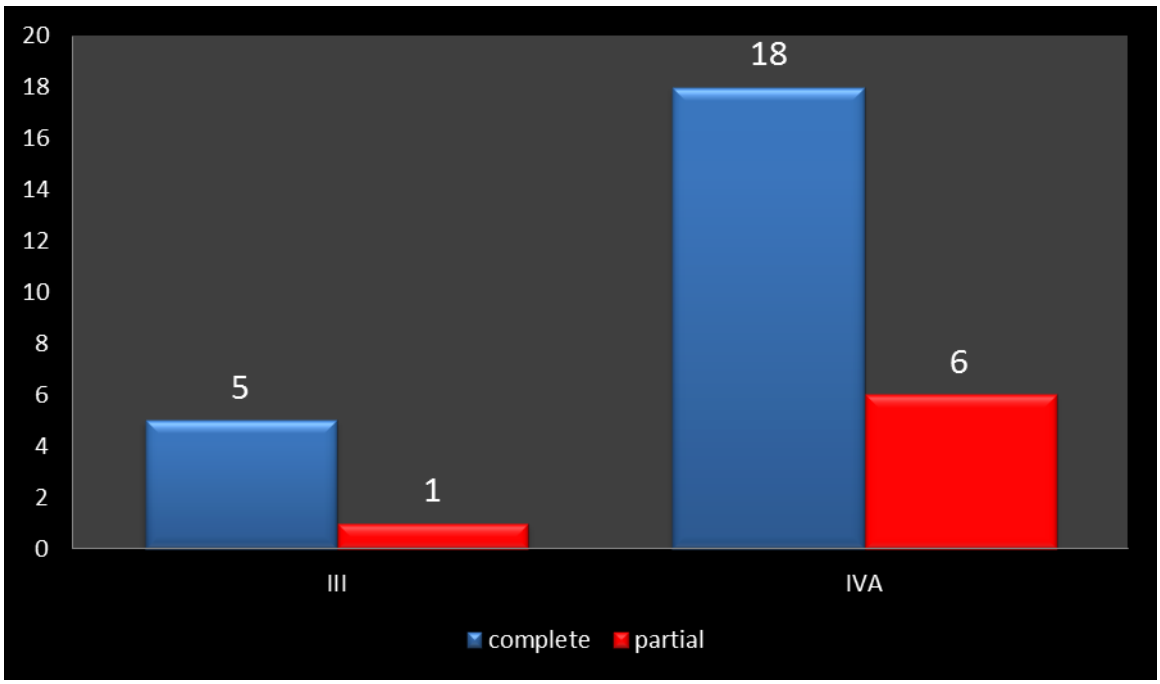


FIG 20 TREATMENT BREAK VS RESPONSE

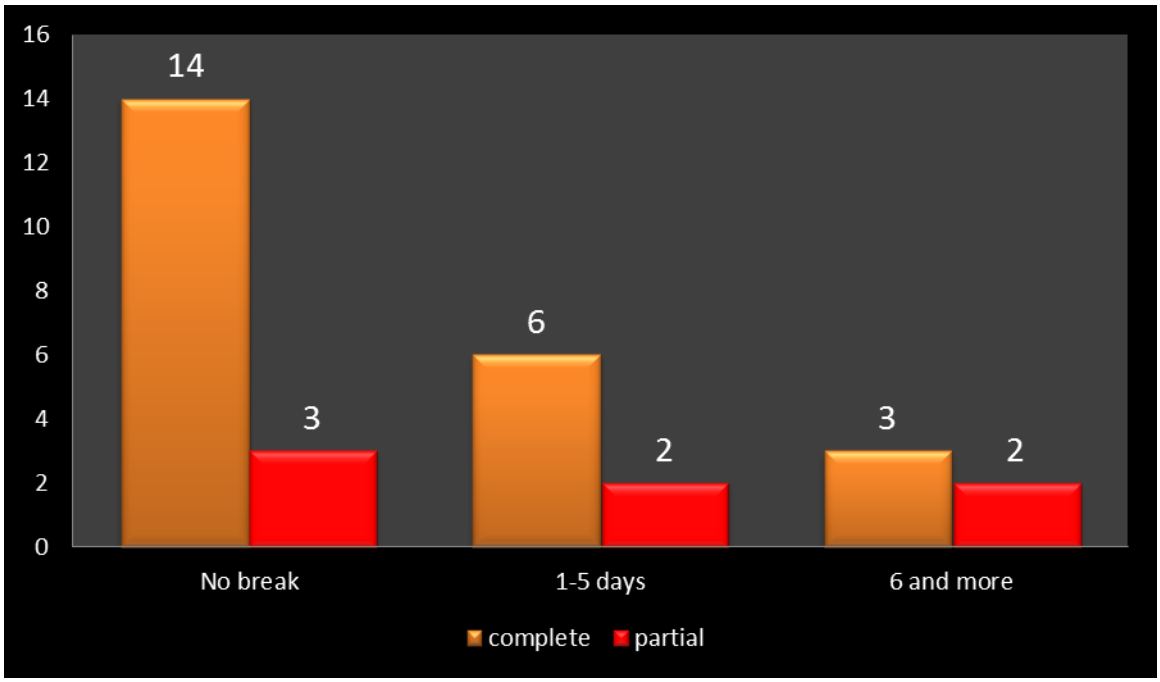


FIG 21 ACUTE TOXICITIES

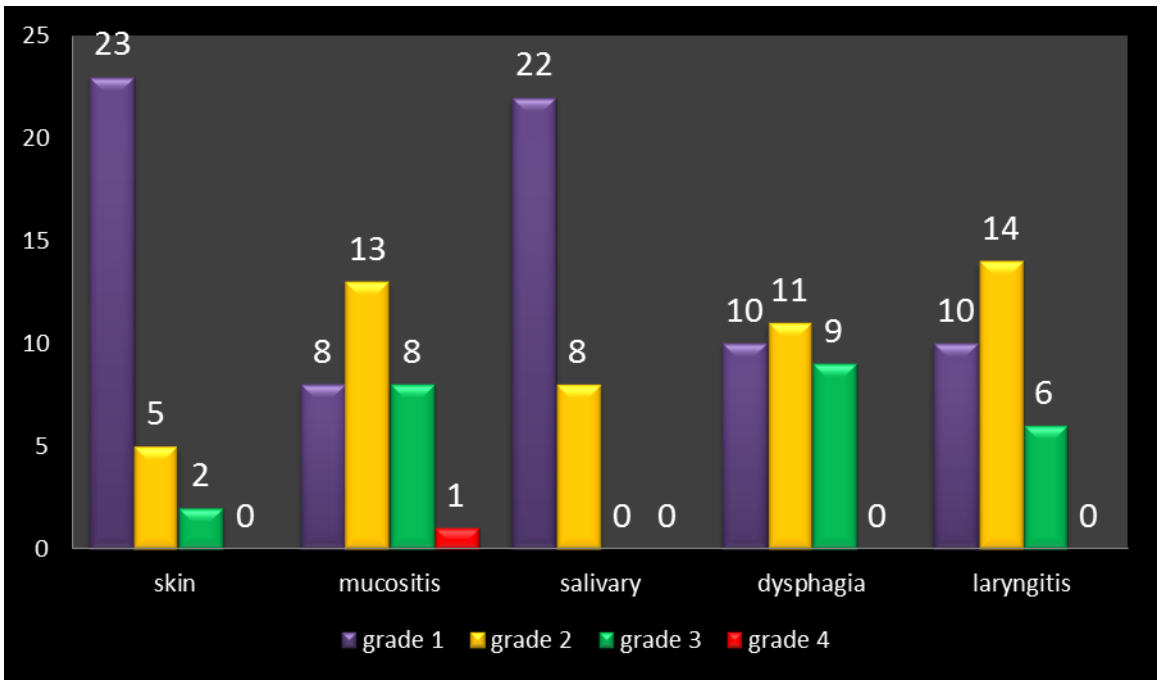


FIG 22 SYSTEMIC TOXICITY

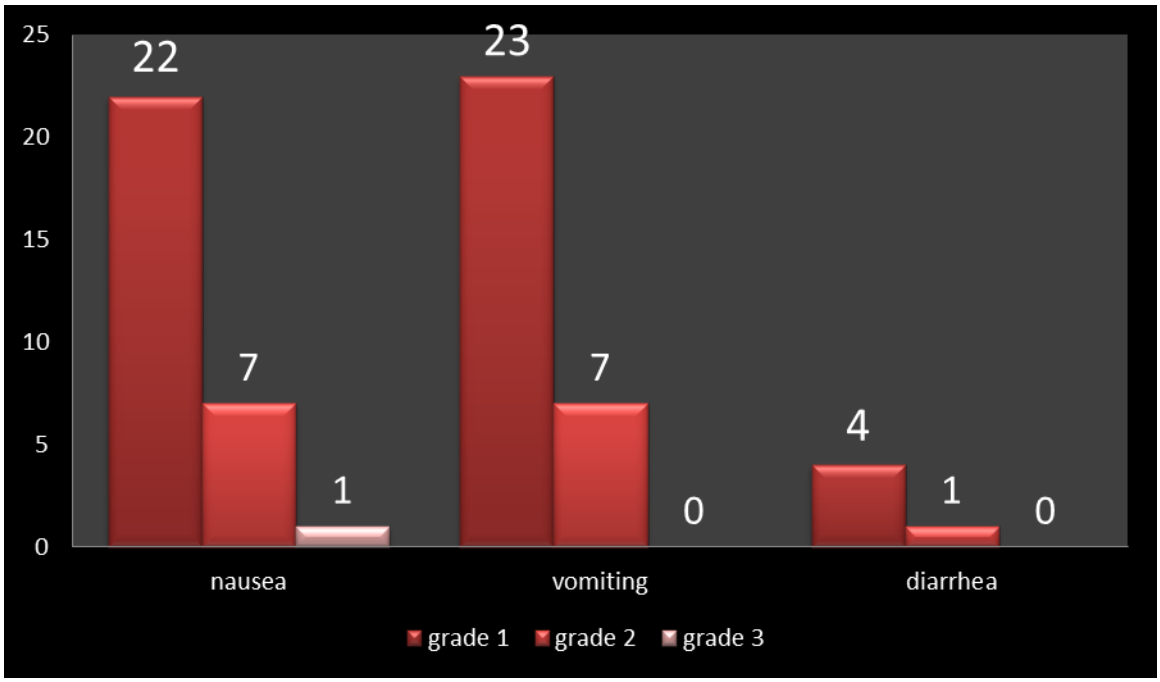
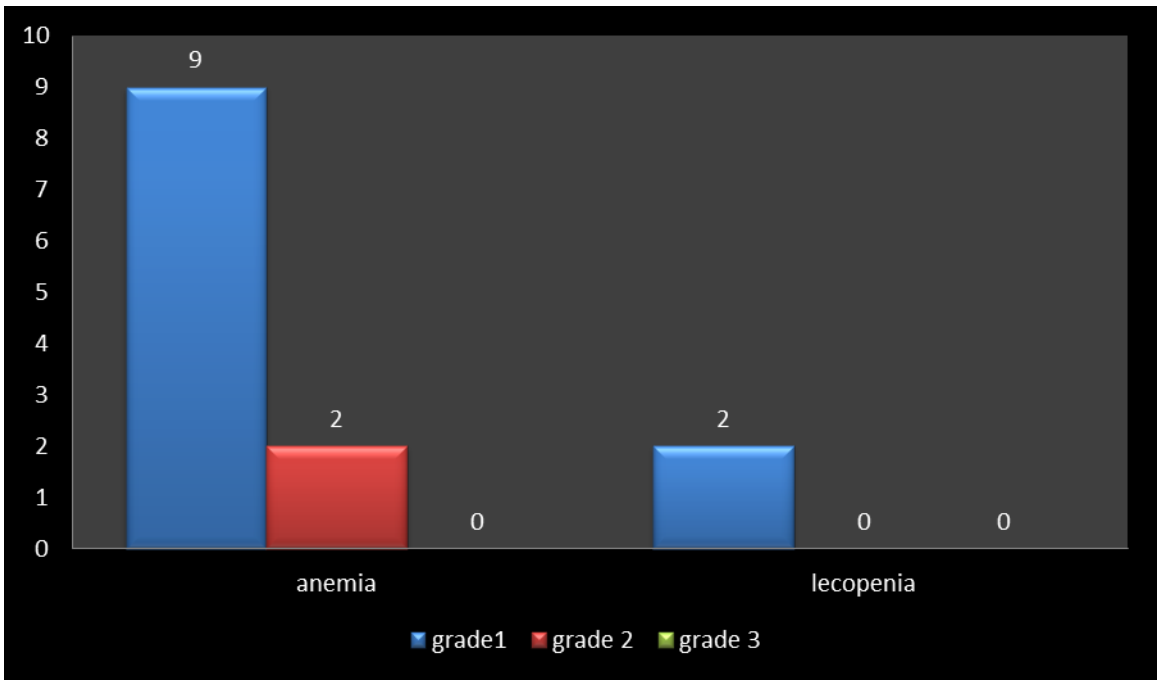


FIG 23 HEMATOLOGICAL TOXICITY



ANNEXURE I

RTOG - ACUTE RADIATION MORBIDITY SCORING CRITERIA

Grade	0	1	2	3	4
Skin	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous Membrane	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Pharynx &Esophagus	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyper alimentation	Complete obstruction, ulceration, perforation, fistula
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste		Acute salivary gland necrosis

Grade	0	1	2	3	4
		such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals			
Laryngitis	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

HEMATOLOGICAL TOXICITY

Grade	0	1	2	3	4
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
0HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-

ANNEXURE II

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS CTCAE VERSION 4.

GRADE	1	2	3	4	5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition.	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated.	-	-
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	>/=6 episodes (separated by 5 minutes) in 24 hrs,tubefeeding, TPN or hospitalization indicated	Life-threatening consequences,urgent intervention indicated	death
Diarrhea	Increase of <4stools per day over baseline	Increase of 4-6 stools per day over the baseline	Increase of >= 7 stools per day over the baseline, incontinence, hospitilisation required	Life threatening consequences. Urgent intervention required	Death
Rash	Macules/papules involving<10 % of BSA with or without symptoms like pain, pruritus	Macules/papules involving 10-3-% of BSA with or without stmptoms	Macules/papules involving >30% of BSA with or without symptoms. Limiting instrumental ADL	Macules/ papules involving abd % if the body surface which may or may not abe associated with symptoms of ruritus or tenderness, associated with severe superinfection requiring iv antibiotics	death

INFORMATION TO PARTICIPANTS

TITLE:CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH GEFITINIB AND CISPLATIN

Principal investigator: Dr. Aoakhum Kichu

Name of the participant:

Site: Department of Radiotherapy, Madras Medical college & RGGGH, Chennai-3

You are invited to take part in the research/study/procedure. The information in this document is meant to help you whether or not to take part. Please feel free to ask if any queries.

What is the purpose of the study? The incidence of head and neck cancer has been increasing worldwide. And local recurrence is a major problem after intensive curative treatment. With our treatment methodology we are aiming to give a better quality of life for the disease by achieving a better immediate locoregional response and less treatment related toxicity. We have obtained permission from the institutional Ethics committee.

The study design: single arm prospective study

Study procedures: patients will need to undergo blood investigations, CT scan neck, x-ray chest, dental prophylaxis and smoking cessation counselling if patient is a smoker. These test are essential to assess the status of the disease. Patients are treated with radiation in conventional regimen over 6-7 weeks. Patients will also receive weekly chemotherapy in the form of cisplatin and daily tablet gefitinib 250mg. Toxicity and response will be assessed during the treatment as well as after the completion of treatment after a period of 6 weeks. Apart from a clinical examination, a laryngoscopy and CT scan will also be done. These test are essential to assess the efficacy of treatment.

Possible Risks to You: non greater than patients receiving standard chemoradiotherapy

Possible Benefits to you: Better response of the tumour to treatment

Possible benefits to other people: The results of the research may provide benefit to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

Confidentiality of the information obtained from you: you have the right to confidentiality regarding the privacy of your medical information (personal details, physical examination, investigations and your medical history). By signing this document you will be allowing the research team investigators, other study personnel, institutional ethics committee and any person or agency required by the law like the drug controller general of India to review your data, if required. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision to not participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be take care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at time during the curse of the study without giving any reasons. You still continue to receive the standard treatment if you decide so. However it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc

Signature of the investigator **Signature of the participant**

Date: Date

INFORMED CONSENT FORM

TITLE OF THE STUDY**:** "CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH GEFITINIB AND CISPLATIN"

NAME OF THE PARTICIPANT:
NAME OF THE PRINCIPAL (Co – Investigator) : DR. Aoakhum Kichu,
NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising myfree power of choice, hereby give my consent to be included as a participant in "CONCURRENT CHEMORADIOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK WITH GEFITINIB AND CISPLATIN"

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer
unusual symptoms. *****
8. I have not participated in any research study within the past 12month(s). *****
9. I agree to under go complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent

Name _____ Signature_____ Date_____

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு

தலை மற்றும் கழுத்துப் பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு நோய்க்குறி தனிப்பு கதிர்வீச்ச சிகிச்சையுடன் கதிர்வீச்சின் பயனை அதிகரிக்கக் கூடிய நெப்டினிப் மற்றும் சின்பிளாட்டின் எனும் மருந்து செலுத்துதல்.

ஆய்வாளர் :

பங்கேற்பாளர்:

இந்த ஆய்வு ராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெற உள்ளது. நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இதிலுள்ள தகவலின் அடிப்படையில் இந்த ஆய்வில் பங்கேற்பதா அல்லது வேண்டாமா என்று நீங்கள் முடிவு செய்து கொள்ளலாம். உங்களது சந்தேகங்களை எங்களிடம் கேட்டு நிவர்த்தி செய்து கொள்ளலாம்.

இந்த ஆய்வின் நோக்கம்:

மாறிவரும் பொருளாதார காரணிகள் மற்றும் வாழ்க்கைமுறையின் காரணமாக தலை மற்றும் கழுத்துப்பகுதி புற்றுநோயினால் பாதிக்கப்பட்டவர்களின் எண்ணிக்கை சமீபகாலமாக அதிகரித்துக்கொண்டே வருகிறது.

பெரும்பாலானோர் இந்த நோய் முற்றிய நிலையிலேயே மருத்துவமனைக்கு வருகின்றனர். அதனால் முழுவதும் குணப்படுத்தக்கூடிய வைத்திய முறைகளை பயன்படுத்தும் வாய்ப்பை இழக்கின்றனர். அதனால் நோய்க்குறி தனிப்பு வைத்திய முறைகளை மட்டுமே பயன்படுத்தும் நிலைக்கு ஆளாகின்றனர். இவ்வகையான வைத்தியத்தில் பலவகை உள்ளன. இந்த ஆய்வில் பயன்படுத்தும் வைத்திய முறையின் மூலம் சிறந்த நோய்க்குறி தனிப்பையும் குறைவான பின்விளைவுகளையும் பெரும் வகையில் வழி செய்வதே எங்கள் நோக்கமாகும்.

ஆய்வின் செயல்முறை:

நோயாளிகள் இரத்தப் பரிசோதனை, முகம் மற்றும் கழுத்துப்பகுதி சிடிஸ்கேன், நெஞ்சப்பகுதி எக்ஸ்-ரே, பல் சுத்தம் மற்றும் பாதுகாப்பு புகைப்படக்கருவி கைவிட ஆலோசனை முதலியவற்றை மேற்கொள்ள வேண்டும். இவை அனைத்தும் வழக்கமாக எல்லா புற்றுநோயாளிகளிடமும் நோயின் நிலையை அறிய மேற்கொள்ளபடுவது. நோயாளிகளுக்கு 5நாட்கள் 6 வாரங்களுக்கு நோய்குறி தனிப்பு கதிர்வீச்சுடன் தினமும் நெப்டினிப் மாத்திரை மற்றும் சின்பிளாட்டின் எனும் மருந்தும் செலுத்தப்படும்.

ஆறு வாரங்கள் கழித்து நோயின் நிலையை அறிய சிடிஸ்கேன் மற்றும் உடல் பரிசோதனை செய்யப்படும். இந்த பரிசோதனைகள் இவ்வகையான வைத்தியத்தின் விளைவுகள் மற்றும் பயன்களை அறிய அவசியம்.

ஆய்வினால் ஏற்படும் நன்மைகள்

சிறந்த நோய்க்குறி தணிப்பும், முறைவான பின்னிணைவுகளும் கிடைக்க அதிக வாய்ப்புகள் உள்ளன.

ஆய்வினால் ஏற்படும் தீமைகள்

வழக்கமான சுதர்வீச்சுகளில் வரும் விளைவுகளைவிட அதிகம் ஏதுமில்லை.

ஆய்வினால் பிறருக்கு ஏற்படும் நன்மைகள்:

இந்த ஆய்வில் கலந்துகொள்வதன் மூலமாக நீங்கள் நோயின் தன்மையில் முன்னேற்றம் பெறலாம். மேலும் வருங்காலத்தில் பிற நோயாளிகளும் பயன்பெற இந்த ஆய்வு உதவியாக அமையும்.

மருத்துவ சிகிச்சையின் தகவல்கள் குறித்த விவரங்கள்:

உங்கள் மருத்துவ சிகிச்சை குறித்த தகவல்கள் ரகசியமாக பாதுகாக்கப்படும்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுக்கு பரிசோதனைகள் செய்து அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :

இடம் :

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

தலை மற்றும் கழுத்துப்பகுதியில் மிகவும் முற்றிய புற்றுநோய்க்கு நோய்க்குறி தனிப்பு கதிர்வீச்சு சிகிச்சையுடன் கதிர்வீச்சின் பயனை அதிகரிக்கக்கூடிய ஜெப்டினிப் மற்றும் சிஸ்பிளாட்டின் எனும் மருந்து செலுத்துதல்

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துக்கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சையும் அதனுடன் வாரம் ஒரு முறை சிஸ்பிளாட்டின் மற்றும் தினசரி ஜெப்டினிப் மருந்தும் எடுத்துக் கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் நான் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் தலை மற்றும் கழுத்து பகுதியில் முற்றிய புற்றுநோய் குறித்த இந்த ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக்கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியின்படி கதிர்வீச்சு சிகிச்சை மற்றும் புற்றுநோய் மருந்துகள் பெற்றுக்கொள்ள சம்மதம். இந்த ஆராய்ச்சிக்கு தேவையான பிற பரிசோதனைகள் செய்துக்கொள்ள சம்மதம்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

நாள் :

இடம் : கையொப்பம்

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Aoakhum Kichu
Postgraduate M.D.(Radio Therapy)
Madras Medical College
Chennai 600 113

Dear Dr.Aoakhum Kichu,

The Institutional Ethics Committee has considered your request and approved your study titled **"Concurrent Chemoradiation in locally advanced head and neck squamous cell carcinoma with cisplatin and gefitinib" No.06032015.**

The following members of Ethics Committee were present in the meeting held on 03.03.2015 conducted at Madras Medical College, Chennai-3.

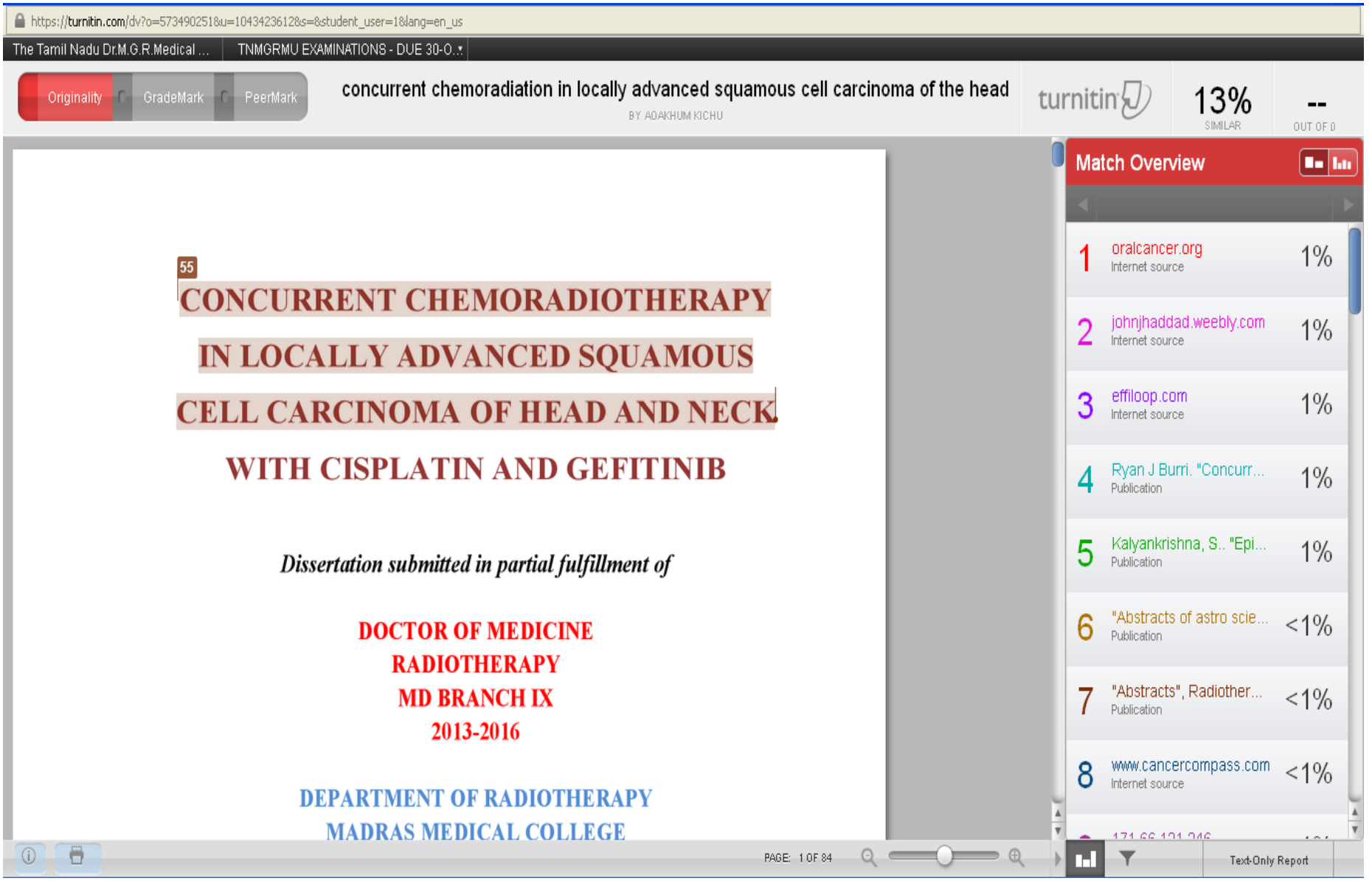
1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D.,Director i/c Institute of Internal Medicine, MMC, Ch-3	: Member
10.Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

9/3/15

Member Secretary, Ethics Committee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